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NUTRITIONAL SURVEYS OF POPULATION GROUPS*

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IT IS SAID that people who live in glass houses should not throw stones. Having perforce spent much time in recent years carrying out nutritional surveys, I might be chary of criticizing them. But since I have now ceased to be actively concerned in their conduct, I can safely attempt to assess their value and define their limitations. John Clarence Cutter was, we are told, "energetic and possessed of forcible character. He had the courage of his convictions, and his fearlessness counted much. . . ." If in giving this lecture one hundred years after his birth I appear to speak more forthrightly than is customary on these august occasions, I would plead that he would have wished a lecturer to do so.

The lecture is on preventive medicine, and we might do well to recall that this subject is not perhaps a branch of medicine, which by derivation is the discipline of healing; and healing or medicine does not arise if prevention of disease is perfect. Most of us who study and teach the normal functions of the human body find such activities to be sterile unless we encroach on pathology. Conversely, those who are skilled in prevention of disease must know the normal state of the body and how it may be altered in different environmental circumstances to allow disease. Unfortunately man is a neglected animal, so far as nutrition is concerned; at the end of the last peace there was no Institute of Human Nutrition in Great Britain, although there were some excellent ones for the study of the nutrition of lower animals. The reason, I think, is to be seen from a quick survey of the rise of nutritional science, for which I crave your indulgence.

For convenience let us look at the history of nutrition on a logarithmic scale of years. Five log. years ago (more correctly antilog. 5), that is, about 100,000 B.C., paleolithic man was a hunter, eating the animals around him and his family and being eaten by them. Four log. years ago, about 10,000 B.C., the neolithic tribe was pastoral, having tamed animals and learned to take their flocks with them on the nomadic search for new pastures. Nutritional problems were probably not common; a hostile tribe would, if victorious, kill you and annex your flocks. Three log. years ago saw at its distal end the rise of agriculture; communities became stationary and famines appeared if crops failed; the Tosorthus stele of about 3000 B.C. described a disastrous famine caused by the failure, seven years in succession, of the Nile to flood. At the near end of our three log. years we have the beginnings of nutritional science: About 250 B.C. Erasistratus did excellent metabolic work on chickens (Dr. Stare here is doing the same on ducks, 2200 years later), and about 200 A.D. Galen was studying the principles of dietetics in gladiators (with the same aim as the Harvard Fatigue Laboratory, before it was recently closed). Between two and two-and-a-half log. years ago there was a period of very great importance, starting with the Renaissance and ending with Darwin. Let us examine briefly two instants in this period of two hundred and one hundred years ago.

In 1753 James Lind published his classical work, "A Treatise of The Scurvy." He first reviewed the literature:

> But as it is no easy matter to root out old prejudices, or to overturn opinions which have acquired an establishment by time, custom, and great authorities; it became therefore requisite for this purpose, to exhibit a full and impartial view of what has hitherto been published on the scurvy. . . . Indeed before this subject could be set in a clear and proper light, it was necessary to remove a great deal of rubbish.

(These words might well be applied to nutritional surveys; before they can be set in a clear and proper light it is necessary to remove a great deal of rubbish.) He then described the disease of scurvy; its symptoms, signs and pathology; its causes, prevention and cure. He based his statements upon accurate observation and well designed experiment (as when on May 20, 1747, he took 12 patients with scurvy, divided them into six groups, and gave each group daily one of the following: a quart of vinegar, half a pint of sea-water, a barley-water electary, or two oranges and a lemon). A few years later a young doctor, William Stark, did some excellent experimental work upon himself. Stark was thirteen years old when Lind published his "Treatise"; he

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graduated at Glasgow and Leiden, and studied in London under John Hunter. He became interested in the function of foods, and on June 12, 1769, he started to study on himself the effects of experimental diets.[1] He did four main experiments in which he produced scurvy in himself and cured it, once with half-a-pint of black currants (containing some 600 mg. of vitamin C). In his final and fatal experiment he intended to try the effects of fresh fruit and vegetables; however, he made his one false step, for he consulted Sir John Pringle, shortly to become president of the Royal Society, who advised him to omit salt from his diet; Stark followed the "rubbish" of "great authorities," castigated by Lind seventeen years earlier, and died at the age of twenty-nine. Had Stark been less unlucky the whole history of nutrition and indeed of medicine might have been changed. There was need for experiments such as his, although they were handicapped by lack of chemical knowledge, — and here again there was bad luck. Some Dutch merchants, who were losing trade in the East Indies through scurvy, had taken the enlightened step of founding a chair of chemistry at Leipzig for the study of antiscorbutics. The person appointed, Michael, had to send his preparations to the Dutch East Indies to be assayed on scorbutic sailors and to await the results months later. He found an oil extract of the seeds of scurvy-grass to be the most effective remedy. With any other vitamin than the unstable vitamin C his approach would probably have been crowned with brilliant success. The distinguished advances in medicine in the past hundred years that have resulted from the use of chemical experimentation might have occurred much earlier if a little luck had helped Michael and Stark.

One may wonder why experiments upon lower animals were not used by these scientists. The relevance of such research to medicine was forgotten until Darwin's work a century later. From then onwards the use of the experimental method upon man and when necessary upon lower animals, together with the advance of chemistry, brought rapid progress in nutritional science.

Finally I come to the last period, one log. year ago, namely, the beginning of 1941. This is when the Oxford Nutrition Survey started — an event of no historical importance whatever but one of some slight personal interest to me, since I was rudely cast from the relatively straightforward discipline of experimental nutritional science into the complicated field of nutritional epidemiology — a subject recently adorned by an interesting review by our chairman, Dr. Gordon.[2] Before describing our own work I must ask you to consider the origin of nutritional surveys, and their purpose and conduct. I shall consider at the end of this lecture their relation to nutritional science.

Origin of Nutritional Surveys

Before the present century there were many attempts to define what food was needed under various conditions, and some were made to determine this experimentally; we have, for instance, already noted the work of William Stark. For reasons we need not pause now to consider there were almost no attempts to investigate the epidemiology of malnutriture, — except in times of famine.

There were sporadic attempts to measure the food consumed by individuals. One of the most interesting was carried out by John Dalton of atomic-theory fame, who in 1831 briefly described certain experiments he had performed as a young man nearly forty years earlier in which at three different seasons of the year he weighed the individual solids and liquids taken at each meal. It is obvious that there was little interest in what food people ate until one could state the composition of that food and compare the data with what they should eat. From the middle of the last century, when food analyses became available, a number of persons (Moleschott in Italy, Playfair in England, Voit following Liebig in Germany, Payen in France, and Atwater in the United States) evolved dietary standards in terms of aliments, and attempts were made to compare the amounts consumed with the standards. For instance, in 1894 Atwater[3] found that, in the United States, daily calorie consumption could vary between the 1490 kilocalories of five Javanese at the World's Fair, Chicago, to the 8850 kilocalories of 237 brickmakers living in a boarding-house in this city of Boston. In Great Britain pioneer work on dietary surveys was done by Charles Booth (1889–1902) and Seebohm Rowntree (1901), later by Orr and by Cathcart and more recently by Widdowson and many others. In the United States the work of Atwater (1886 and onwards) includes some of the best studies ever made in human nutrition; later dietary surveys were made by Sherman and Gillett (1914–1915), Stiebeling and Phipard (1939), Dr. Stare and his colleagues and many others, and a large number of dietary studies have now been made in different countries.

Observations about height and weight, fatness, and clinical signs were soon added. Koppe (1905)[4] rated the amount of subcutaneous fat in five grades as one of the eight components of constitution. To subcutaneous fat Gastpar (1908)[5] added pallor of skin and mucous membranes, and muscle bulk. Hogarth (1909)[6] rated the nutriture of school children according to muscle bulk and subcutaneous fat; Howarth (1910)[7] used three grades according to color of skin and mucous membranes, condition of hair, muscle tone and alertness. Then came the Dunfermline system (Mackenzie, 1912–1913)[8] in England and the Sacratama index of von Pirquet in Austria. The discovery of vitamins brought

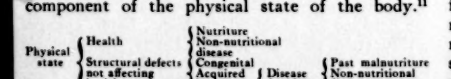
supposedly more specific methods. Thus we find that at the end of 1932 the Health Committee of the League of Nations recommended von Pirquet's Sacratama index together with certain clinical signs of vitamin deficiencies, x-ray films of epiphyseal junctions and determinations of protein in serum and hemoglobin and inorganic phosphate in blood. The methods available were summarized for the League by Bigwood (1939)[9] and were put into practice in various countries at about the time the war started; the most comprehensive ones in this country were the Tennessee survey of Youmans, the North Carolina survey of Milam and the Pennsylvania survey of Mack. Let us pass to consider the methods used in these and other surveys.

The Methods of Nutritional Surveys

We are discussing nutritional surveys of population groups. The purpose of such surveys is to define the cause, severity and distribution of malnutriture; this is achieved by assessing the nutriture of individuals within selected groups. No mass method is available. We must not delude ourselves into believing that we are told anything worth-while about the nutriture of populations by the type of study in which the food consumption of a large group, such as a country, is assessed by estimating food imported and exported, guessing food home produced and dividing by the number of inhabitants suitably adjusted through the use of some arbitrary scale of man-values. Such statistics no doubt have their uses, but not for the assessment of nutriture. We may also pass by minimum-cost studies, in which the amount of money believed to be spent on food is divided by the minimum amount believed to be necessary for purchasing an adequate diet. These studies may interest economists but they do not assess nutriture.

In considering what nutriture is and how it can be assessed I shall follow what I have written elsewhere.[10] I do not think we can usefully consider the methods of nutritional surveys without first considering their purpose.

Nutriture, which is the state of the body or cells resulting from the nutrition of the body or cells, is one of the components of health, and health is a component of the physical state of the body.[11]



This relation is important because, as we shall see, many attempts to assess nutriture in fact assess physical state. Consider two persons, one with a leg missing because of an accident and the other with carious teeth. In neither case could physical state be considered perfect, but health could be perfect if general function was not seriously impaired. My friend Professor John Ryle[12] used to maintain that if an old carious lesion in a tooth were unfilled health could not be perfect, whereas if the cavity were filled health could be perfect. I would regard inactive caries of any type in a tooth as not affecting health unless it seriously impairs general function; if full health could exist after extraction of the tooth or the filling of its cavity, full health can certainly exist while it is there unless some factor such as pain limits function; rats on a diet free of fluorine die of starvation because chewing is painful.[13] Obviously non-nutritional factors that affect health may affect nutriture; the cachexia of carcinoma is an example.

There are three properties of nutriture that are relevant in its assessment: quality, degree and duration. *Quality* expresses the types or kinds of deficiencies of other factors that are affecting nutriture. It therefore includes specificity and takes account of the unfortunate fact that deficiency of each of several nutrients can produce the same clinical sign; angular stomatitis can apparently arise from deficiency of iron or of riboflavin, and Dr. Ramalingaswami and I[14] have found (following earlier work of others on man) that this is an early and consistent sign of pyridoxine deficiency in rats. A clinical sign is often produced by a defect in the nutriture of a cell caused by a break in the metabolic chain in that cell, and deficiencies of one or more nutrients or the presence of one or more poisons may break the chain — even at the same link. One puzzling fact is that lesions produced by combined deficiencies may be very different from the sum of the lesions of the individual deficiencies: Follis[15] showed that deficiency of potassium or of thiamine causes myocardial necrosis, whereas deficiency of these two nutrients together is not accompanied by any pathologic change in the heart. If the assessment of nutriture is to be used in preventive medicine quality must be considered; assessing the quality of malnutriture is essential in defining its cause. Since it is important to distinguish between malnutriture produced by deficiency of aliments and that produced by deficiency of specific nutrients, it is useful to restrict the term "nourishment" to the former.

The severity of malnutriture is defined in terms of its second quality, namely, *degree*. I[10] have defined five degrees: excess nutriture, normal nutriture, poor nutriture, latent malnutriture and clinical malnutriture. We need not consider them now. But severity is more than degree; it includes the last property of nutriture, namely, *duration*. Duration is of course concerned with the time for which the state has existed; since malnutriture of short duration is in general more easily reversed than that of long duration, this affects the severity in population groups. I would call your attention to the confusion that exists in medical literature concerning the use of the terms "acute" and "chronic." The latter is often used to denote a condition that has existed for a long time, — and indeed this is the

derivational and dictionary usage. But we find that the dictionary, — of course I speak of the Oxford English Dictionary, edited by my colleague Dr. Onions, — is inconsistent; it opposes "chronic" to "acute" and therefore we expect to find an acute disease defined as one that is of short duration. We do not. It is one that comes sharply to a point or crisis of severity. We note therefore that a disease with a succession of crises of severity could be simultaneously both acute and chronic. I would suggest that we should regard processes as being short or long, and as having a degree that is changing rapidly or slowly. A rapid change of degree is acuteness; a slow or zero change is chronicity. These terms then do not denote duration, but the first differential coefficient of degree with respect to duration (I[10] have discussed this more fully in my paper in *Vitamins and Hormones*. Kruse[16-18] has, in his concept of the deficiency states, made much use of certain properties he ascribes to the pathologic process in the tissue in a deficiency disease. I think he has added confusion, and I have criticized him elsewhere[10, 19]; I spare you further colloquy on this and pass to consider the third function of a nutritional survey, namely, the assessment of the distribution or incidence of malnutriture. We are here concerned with sampling and with the concept of normality.

Sampling is as important in nutritional surveys as in any other branch of epidemiology. Of the many pitfalls that occur I will select three as examples. In the Netherlands, houses were chosen on a sound statistical basis and all occupants were asked to attend a clinic. Had the apparent refusals not been followed up, the worst cases of malnutriture would have been missed because no person was unwilling to attend but some were too ill to do so. When attending a committee in Germany I was shown the results of a nutritional survey in a certain town and was surprised at the gloomy picture presented. I was assured by the medical officer in charge that they were correct. I asked about the sampling and was shown the letter of instructions sent to the Oberburgermeister. I spoke to him, and he told me that as the army authorities were making a nutritional survey he supposed they would like to see cases of malnutrition, so he sent them as the sample those persons who were to be given extra rations on the grounds of malnutrition. In another town, I watched a street-corner weight survey carried out by an allied sergeant with two GIs and a German interpreter with scales and measuring-rod at a busy street junction. Here nothing but the errors was random. The GIs selected the pretty girls, the interpreter (and the onlookers) discouraged fat Germans and pushed forward thin ones; the bright-eyed healthy streetwalkers came up to see what was going on and were weighed; the listless malnourished passed by on the other side; the worst were at home in bed. Even if one gets a proper sample to examine, troubles are not ended. One may, for instance, be taking a venous blood sample from, and measuring the dark adaptation of, every tenth person clinically examined. A case of suspected vitamin-A deficiency is found and this is not a tenth person. One can scarcely refrain from making further tests to clinch the diagnosis — but one must refrain unless the results are rigidly excluded from the sample. The results obtained on our sample are used for comparison with other samples; we usually grade them as normal or abnormal. The concept of normality was excellently discussed by Ivy[20] and less satisfactorily by Ryle,[12] who was unaware of the former publication; I have commented upon their definitions elsewhere.[10] We must use two definitions of normality in different circumstances, one based on physiologic and the other on statistical concepts. We may say that the condition of the body or of some part or function of the body is (physiologically) normal when it allows the usual functions to be performed in the usual environment. We may also say that a value of a variate is statistically normal when it does not differ from the mean by more than the standard deviation. Unfortunately we have as yet insufficient data concerning the distribution of variates from which the range of normality can be assessed. In the course of the work of the Oxford Nutrition Survey we obtained a large number of such data. We are analyzing them in this way: We can exclude from our estimations all those subjects who were found to have any clinical, dietary or other abnormality that might affect values, and thereby we can obtain the distribution of the variate in normal members of the population.

The assessment of nutriture is a diagnosis and, like clinical diagnosis, it uses various disciplines. The methods used may most conveniently be discussed under four headings: dietary, chemical, functional and clinical methods. These reflect the order in which deficiency is likely to arise; the person partakes of an inadequate diet, which may be detected by dietary methods. Later a change occurs in the concentration of nutrients (such as ascorbic acid) or of metabolites (such as pyruvate), or of compounds found through the agency of the nutrients (such as hemoglobin), and these may be detected by chemical methods. Later, changes in function may be found. Lastly, morphologic changes in tissues may occur, and these may be detected by what we shall for convenience call clinical methods.

I[10] have pointed out elsewhere that dietary methods cannot usually alone be used to assess nutriture, but a dietary history is an essential part of such an assessment and must be included even in rapid nutritional surveys. The purpose of including dietary information is to aid in interpreting the cause of, and suggesting a remedy for, any malnutriture that may be found. The difficulties of obtaining

accurate dietary information have often been underestimated; for instance, the housewife may wish to show her efficiency, or she may hope to prove shortage of food, and not infrequently she cannot be bothered accurately to fill in the formidable array of forms that are presented to her. The errors involved in the computation of the nutrient content of diets are not always appreciated. We have spent much time in evolving a foolproof method of calculating dietaries; for this and for other purposes we have used a nutritional unit based partly on the share system of Dr. Mary Swartz Rose; this unit we call the Atwater.[21] Finally, even when the nutrient content of a diet is known difficulties arise in assessing availability and requirements.

Chemical methods are very valuable even in rapid field surveys. Their use has not been fully appreciated, — partly because they were introduced for public-health purposes before their interpretation had been investigated experimentally and partly because it is supposed that complicated and expensive apparatus is needed. We still know comparatively little about the interpretation of estimations of substances in the tissues, blood and urine. Since the composition of tissues alters before structural changes occur through malnutriture, estimations of vitamins of the B complex (thiamine, riboflavin, niacin and pyridoxine) and of ascorbic acid in tissues such as leukocytes are particularly useful. Compounds in plasma vary in their behavior: Some, such as carotenoids and ascorbic acid, tend to reflect the immediate past intake; others, such as niacin and riboflavin and, usually, protein, remain at concentrations that are within the statistically normal range even though clinical malnutriture may be present; therefore in these cases a single estimation that falls within the statistically normal range gives little information. Estimations upon urine, with or without test doses, have not yet been proved valuable for assessing nutriture.

The only functional method that has so far proved valuable is the measurement of the rod threshold of the dark-adapted eye, provided that retesting after therapy with vitamin A is included. There are many factors other than nutrition, and there are nutritional factors other than vitamin A, that affect this measurement. Since endurance is affected by malnutriture, particularly by undernourishment, objective tests of this would be useful; unfortunately such a test, that would be applicable in a nutritional survey of a population group and that would scarcely be affected by variations in strength and motivation, has not yet been devised.

We will, I think, all be agreed that clinical methods are essential in the proper assessment of nutriture, and we may here include somatometric methods, such as the use of sex-age-height-weight tables. These, and the calculation of various indices based on body measurements, are by themselves useless in the cross-sectional assessment of nutriture in an individual, although the measurements of height and weight and of the thickness of skin and subcutaneous tissue are useful in nutritional surveys. Although I speak with some hesitation about the growth of children in Boston, where Dr. Harold Stuart has carried out such valuable studies, I think we should bear in mind that the optimum rate of growth of children is not necessarily the maximum, and that harm may be done by excessive feeding of children with milk or school meals and now by medication with vitamin B_{12} and aureomycin, even though these activities make them grow more quickly and mature earlier. I have already mentioned the introduction of the general assessment of nutriture by inspection soon after the start of this century: In Great Britain it was adopted by the Board of Education in 1907, extended by the Dunfermline system a few years later[9] and revised in 1934; it is still used by many school medical officers. There is no doubt that the method assesses muscular development and physique more than general nutriture and, as shown admirably by Jones,[22] experienced school medical officers are not consistent with one another or even with themselves. Our Ministry of Health has continued such surveys with modification, and I have criticized these in detail elsewhere.[10, 11] The clinical assessment must include a medical history in which symptoms, though subjective, will be recorded. Examination of clinical signs must take into account all the non-nutritional factors that may produce them; the interpretation of clinical signs is exceptionally difficult because almost all the early signs are unspecific. The tissues that are most often affected structurally in malnutriture are the epidermis and the cornea; this statement is not derived entirely from the fact that few other tissues can be inspected but is based upon post-mortem examinations of man and lower animals.

It is by a combination of the methods just outlined that the diagnosis of the estimation of nutriture must be made; this is not necessarily a formidable procedure, as I hope to show you by the following brief account of our own work.

The Oxford Nutrition Survey

The Oxford Nutrition Survey started early in 1941 at the request of the Ministry of Health and with the support of the Ministry of Food and the Medical Research Council. It began in a hurry, since the Ministry of Food happened to be conducting a dietary survey in Oxford and it was desirable to link with this the more detailed studies that were projected. Since governmental funds are slow to mobilize, it ran for its first few months without financial support; it was accommodated in the university's Department of Biochemistry through the kindness of professor R. A. Peters. Soon it was put on a secure basis by the generous

financial assistance of the International Health Division of the Rockefeller Foundation.

At this time there was a tendency for those not immediately connected with nutritional research to believe that the methods of nutritional surveys had been established and that all that was required was a team to apply them. We did not accept this view. We therefore decided in our initial surveys to include all reasonable methods of assessing nutriture so that we could test their efficacy and select those most valuable. These initial surveys were made on working-class families in and around Oxford. Such surveys, essential through they were, did not give the rapid answers expected and required by governmental officials. Mobile surveys were therefore started by a group that consisted initially of a clinician (Dr. A. P. Meiklejohn), a dietitian and a biochemist. This team went to areas selected by the Ministry of Health, where families were investigated, samples of blood being dispatched to Oxford for some of the analyses. Initially this type of survey was also slower than required by the authorities; information was therefore obtained from two further sources: rapid clinical surveys and large-scale biochemical analyses upon samples of blood obtained by the Blood Transfusion Services.

The first rapid clinical survey was made in response to a specific problem: it was alleged that deficiency of riboflavin was prevalent in the Royal Navy, and we therefore organized early in 1942 a survey in which 1373 naval ratings in various parts of the country were examined clinically for the early signs of nutritional deficiency, were examined with a slit-lamp microscope for superficial corneal vascularisation and were tested for night vision. We were most fortunate in being joined by Dr. Sydenstricker just as the survey was about to start; without his authoritative views upon the supposed early signs of deficiency of riboflavin, our survey would have given no trustworthy answer. Thereafter Dr. Sydenstricker conducted rapid nutritional surveys throughout the country; he[23] has described these in outline. His technic was essentially a rapid inspection of the skin, hair, tongue and mucous membranes of the mouth and a slit-lamp examination of the cornea and scleral conjunctiva; he also recorded certain data about the teeth, including the presence of dentures. In addition, he noted what he called "general physical status," dividing it into "good," "satisfactory" and "poor." He made no general physical examination and performed no laboratory tests. As I have mentioned elsewhere,[11] it was invaluable to have Dr. Sydenstricker in Great Britain during the war to reassure us about the nutriture of the population by showing that there was a low incidence of the clinical signs he sought; there was and is no greater authority upon those signs. I consider, however, that such surveys are by themselves inadequate for public-health purposes in England in peace, since they do not detect early malnutriture.

It was important during the war to be able to detect as early as possible any trends that might be occurring in the nutriture of the population, particularly concerning certain nutrients like ascorbic acid, of which the dietary levels were considerably affected by import policy. For this purpose we included large-scale analyses of blood samples obtained with the co-operation of a former Cutter Lecturer, Sir Lionel Whitby. The Army Blood Transfusion Service under him sent teams to various localities, where volunteers were bled. A small sample of this blood was at once sent to us at Oxford and analyzed for hemoglobin, protein, vitamin A and ascorbic acid. We fully appreciated from the experience of others and from our own investigations that samples of blood taken from a recumbent donor with a tourniquet on his arm, even if the first portion of the blood was reserved for us, would not give analyses that would approach the customary standard of accuracy. Our purpose, however, was not this. We wished to obtain a rough idea of trends that might be occurring in fairly comparable population groups at different seasons of the year, and of different mean levels between such population groups. We were able to obtain for each sample data about age, sex, locality and occupation of the donor.

While these four survey methods were being used in England, a limited amount of research was undertaken to examine some of the methods, and special groups of the population or of the Armed Forces were investigated as required. Toward the end of the war we turned our attention to the possibility of making surveys in liberated parts of Europe so that the distribution of food, whether carried out by the Army, UNNRA or, later, by the national governments, might be made according to certain priorities; since, in an area of malnutriture, the distribution of limited foodstuffs must be according to need, the problem is to discover who is in greatest need and the nature of that need. We set forth in 1944 the methods that should be used and received generous financial assistance from the Rockefeller Foundation for equipping two mobile laboratories for such work. In response to an invitation from the government of the Netherlands, these laboratories, with members of our staff, went shortly before the end of the war to study the acute famine in the Western Netherlands. In this work, of which a preliminary account has been published,[24] we were greatly assisted by the skilled help of colleagues in the Netherlands. Thereafter we conducted nutritional surveys in the British Zone of Germany. We hope shortly to publish in detail the results, in which we shall be able to compare and contrast the findings upon a comparatively well nourished population as in wartime Britain, a population subjected to an acute famine as in the Netherlands

in April and May, 1945, and a population in which there was chronic malnutriture as in Germany immediately after the war.

We are convinced, as a result of our experience, particularly in the Netherlands and in Germany, that a team consisting of a clinician, a biochemist, a dietist, a technician and a clerk can carry out rapid nutritional surveys of population groups by a combination of clinical, biochemical, functional and dietary methods and can report without delay their results to the relevant authorities. It remains to consider who those authorities are and the auspices under which such surveys should be conducted.

The Place of Nutritional Surveys in the University and in Public-Health Practice

In this section I shall speak of my own country, for I do not presume to know — still less to understand — the relative responsibilities of state and Federal organizations here, — and if I did, it would be impertinent of me to comment.

The object of any science is the accumulation of systematized verifiable knowledge; this is achieved through observation, experiment and thought (which includes both criticism and imagination). Experiment is observation under controlled conditions. Observation (by which I mean bare observation) played an important part in primitive nutritional science: our ancestors observed that certain berries produced stomach-ache; we observe that they contain vitamin C. Progress only became rapid when medical science adopted the much more efficient tool of experiment. Though Galen devised brilliant physiologic experiments and almost discovered the circulation of the blood, his method was lost in the Dark Ages. The importance of Harvey is that he restored to medical science the study of function by deliberately planned experiment; that, no doubt, was why Sir Thomas Browne wrote that he "preferred the circulation of the blood to the discovery of America." We have seen earlier in this lecture the experimental work of Michael, Lind and Stark; we may also note that Lind's work was put into practice by the Admiralty after forty years and by the Mercantile Marine almost a century after his work. The use of the experimental method has brilliant discoveries to its credit, whereas the method of observation has achieved little. The observer must await the occurrence of the natural succession of events he wishes to study, and he is very apt to be misled by the fallacy of *post hoc ergo propter hoc* or by the existence of a correlation without causality. Nutritional science should be studied as a branch of experimental science. Human nutritional science is a branch of fundamental science that studies nutrition in man experimentally, whether on patients with developed malnutriture or on volunteers in whom malnutriture is induced. It has recourse to experiments upon lower animals to supplement experiments on man. The importance of the experimental approach I learned from the master at whose feet I sat — Charles Sherrington (still fortunately among us). When an Institute of Social Medicine was projected in Oxford I hoped the nutritional work we were doing would be included in it, for social medicine could scarcely be studied without reference to nutrition. The Regius Professor of Physics at Cambridge, John Ryle, was appointed its professor. He had, in several articles and in his research at Cambridge, extolled the observational as opposed to the experimental method, crossing swords with Sir Thomas Lewis. When Ryle told me that no experiments, either upon man or upon lower animals, would be done in the Institute of Social Medicine, I decided that human nutrition could not be usefully studied there. I have in consequence been said to have quarreled with Ryle. He assured me, and I know, that there was no quarrel. He was a great clinician whose wise counsel and inspiring friendship I treasured. His memory I treasure. We shared a desire to advance medicine and we differed seriously only in our approach to that end.

Medicine, like agriculture or engineering, rests with shifting emphasis upon a tripod, the three limbs of which are a practical art, a theoretical science and an applied science. The theoretical science derives from two sources. First, there are the fundamental sciences of human physiology, biochemistry and the like; secondly, there is clinical science. Both study man experimentally and both have recourse to experiments upon lower animals. Both are proper subjects of study in a university. The main difference between the two is that in the fundamental sciences knowledge is pursued for its own sake, whereas the object of clinical science is to elucidate disease. The distinction between the two is often slight; the science of human nutrition may include either or both. For instance, we may study the human dietary requirements, metabolism and bodily functions of silver without supposing that silver deficiency ("anargyrosis") ever arises in man; that is in the realm of fundamental science. Or we may study the disease Kwashiorkor in the field, in volunteers and in lower animals to elucidate its etiology and establish its therapy; that is in the realm of clinical science. Both, we would all agree, are properly pursued in the university, which is concerned with the advancement of knowledge by research and teaching. We may well ask whether the applied science of nutrition belongs to the universities. I believe it does not. Lind was right in establishing the prevention and cure of scurvy by fruit juice; it was not for him to ensure that the juice was distributed.

In England, as a former Cutter Lecturer has stated elsewhere,[28] it is the duty of the Ministry of Health to advise on nutritional policy, and it is the business of the departments of food and agriculture

to give effect, so far as is practicable, to this policy, either by importing or by producing the foodstuffs required. This was a wise Cabinet decision, since the primary object of agriculture is to produce human food, and the purpose of food is to maintain or promote health. Indeed, one may wonder whether ministries of agriculture and food are necessary. The latter is a recent outgrowth of two World Wars, disappearing in the peace between. The former was started by my great-grandfather, who was its first president, in 1793; with great filial impiety I should like to propose its abolition. If the Ministry of Health is responsible for advising on nutritional policy, it must be informed of the epidemiology of malnutrition in the country. As agreed in 1943 at the United Nations Conference on Food and Agriculture[26] at Hot Springs, "The first step in planning a nutrition program for any country should be to determine the needs of the population for health in terms of the more important nutrients" by making nutritional surveys. The countries that have accepted the unanimous recommendations of the Conference are pledged to undertake immediately such nutritional surveys, to deal by dietary and medical means with any malnutrition discovered and to take steps to prevent its recurrence. They are further pledged to report periodically to the permanent organization upon the results of their investigations into national food habits and nutriture. Two teams might be established by the Ministry of Health for this purpose, each consisting of clinician, biochemist, dietitian, technician and clerk. They would work through the local medical officers of health and be based on a central organization that could carry out certain chemical analyses and assist in computing the results on Hollerith cards so that they would be rapidly available; for this we introduced a punch-card that has been reproduced elsewhere[24] and has, I understand, proved satisfactory in Dr. Pett's surveys in Canada. Apart from the essential epidemiologic information that they provide, such nutritional surveys are very valuable in an educational program because they stimulate a personal interest in nutrition among both the population and the local practitioners of medicine. These teams should be available to undertake any special nutritional problem that arises in the field of public health. An alleged outbreak of scurvy in a town could be investigated at once, but their normal function would be to anticipate any such outbreak. Obviously only valid methods and the latest technics of proved worth must be used. This cannot be ensured by sending the teams out from an office in the Ministry in the center of London, but it can be achieved by locating them near a university institute where active research on human nutrition is in progress. A bureau of human nutrition might link the two, its object being to collect and integrate knowledge relevant to the subject so that its staff, its library and its museum might be consulted by medical officers, hospital dietitians and others anxious to keep in close touch with the advancing front of research; it would exchange information with all the other countries that, by accepting the Final Act of the United Nations Conference on Food and Agriculture,[26] pledge themselves to such an interchange of information.

If we agree, then, that pure science, whether fundamental experimentation or clinical science, belongs in the universities, whereas the application of science does not, we may ask whether nutritional surveys of population groups should be made entirely by public-health agencies or can also find a place in the university. I believe that the function here is strictly limited. We would not deny to the Ministry's teams the right to do research; indeed, this should be encouraged, since they could not efficiently continue to make public-health surveys endlessly. Nor would we deny a university department the right to undertake field research if, — and only if, — new and useful knowledge is likely to result. Goldberger's brilliant research on the epidemiology of pellagra was work that any nutritional scientist might be proud to imitate. Research on similar lines has been and is being done on goiter, fluorosis and Kwashiorkor. It would be extended to study the distribution of disease in relation to diet in various parts of the world, and might well include the detailed and long-term study of improved diet upon a fairly circumscribed community, as on an island. Such research would best be undertaken jointly by two or more university departments, preferably situated in different countries. Your penultimate Cutter Lecturer, Sir James Spence, once wrote as follows[27]:

> The second aspect of the problem (of nutritional assessment) is the group investigation. By this I mean physical examinations or nutritional inquiries in various representative groups of the community. I admit that there is difficulty in getting this type of work carried out satisfactorily. It is clinical research. It requires trained clinical research workers. This in turn needs organization and financial support. The place for all this is surely in the universities and medical schools. It is a pressing need that in some of our universities there should be set up departments for the study of human nutrition. They would be primarily clinical departments, but, having contact with other scientific departments they would serve as centers of research and training. They would test and apply the scientific knowledge of nutrition which comes from departments of physiology and biochemistry. If human nutrition is as important a subject as this meeting suggests it is, it is surely not too much to ask that it should have this recognition in our universities.

One should now, I believe, demur from this. A university institute of human nutrition should work on its own lines of research, using any methods that seem applicable; it should not be testing and applying scientific knowledge of nutrition so much as advancing such knowledge; the application should belong to the Ministry of Health. For there is a danger, even in a university, of dictated research;

the clinician or the medical practitioner who approaches the scientist and asks him to work on a problem may be a menace, since few scientists are at a loss for interesting problems to pursue. And the university scientist will shun the routine organization needed in nutritional surveys.

We see, therefore, that there can be two types of nutritional surveys of population groups: those designed to study the epidemiology of malnutriture and conducted repeatedly by the Ministry of Health, — these are nutritional surveys proper, — and field research, which is used as an occasional tool by the nutritional scientist to advance fundamental knowledge. The two should not be entirely divorced, and indeed might usefully collaborate on occasion in studying malnourished populations abroad. But the observational method of nutritional surveys proper is very unlikely to advance fundamental knowledge of nutritional science and has no place in a university nutritional institute. We were faced in the Netherlands and Germany with the conduct of surveys for the specific and urgent public health purpose of establishing the incidence, cause and severity of malnutriture and then of recommending treatment.

There were therefore no opportunities for the detailed experimental study of a few cases,which is the method of choice for advancing fundamental knowledge. Had we gone with a government team whose function was the conduct of epidemiologic surveys, their normal routine work would have been enlivened by the new experience, and our research would have been possible — but no such team existed. Fortunately, controlled observations on a few persons were made by others on malnourished persons during and after the war.[28] In the future, we may hope that all countries will have such epidemiologic teams and such institutes for experimental research and that there may be constant interchange of information between them and the joint field studies, especially within their own country but also with the corresponding teams and institutes in other countries. There are, unfortunately, large areas of the world where gross malnutriture exists, and surely combined studies by experimental scientists and nutritional epidemiologists should be made. We need close collaboration between the pure and the applied science of human nutrition.

John Clarence Cutter, himself the son of a physiologist, combined a professorship of physiology with a consultant post in a government colonial department. I have tried to assess the role of nutritional surveys in establishing the epidemiology of malnutriture in population groups, such surveys being conducted by teams from the governmental agency responsible for nutritional policy but in close contact with those engaged upon basic research in human nutrition. There is perhaps at the present time no more important field of preventive medicine.

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A COMPARISON OF BLOOD-SUGAR AND URINE-SUGAR DETERMINATIONS FOR THE DETECTION OF DIABETES*

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GENERAL METHOD OF STUDY

DIABETES case-finding activities have been carried on since June, 1947, as part of a community diabetes control program in the town of Brookline, Massachusetts. This town has a population of approximately 58,000. For 3186 persons over 25 years of age, both blood-sugar and urine-sugar determinations were done as initial screening procedures. A screening procedure is a simple test used to divide people into two groups, — one large group of negatives and a smaller group of positives considered to have a high enough index of suspicion to warrant more detailed examination for the disease in question. If the screening test is to be efficient, it must lead to the eventual discovery of a high number of persons with the disease for a given amount of effort expended. The purpose of this report is to examine the findings from this group of 3186 persons in order to compare the relative specificity and efficiency of urine-sugar and blood-sugar determinations as screening procedures for diabetes.

The case-finding procedure used in this study may be divided into three phases: screening, re-examination and diagnosis.

Screening (Phase I)

A capillary blood-sugar determination and urine-sugar determination were performed for all subjects examined. The initial test was performed by members of the Health Department in various locations convenient to community groups. The results of the screening test were used to select persons for whom it would be profitable to do further testing.

Re-examination (Phase II)

The persons selected by this procedure were brought to the Health Department for repeat blood-sugar and urine-sugar determinations and glucose-tolerance tests as indicated. These results were used to establish the presence or absence of persistent hyperglycemia and glycosuria. Sufficient data were obtained to determine whether persons re-examined could be classified in one of the following categories:

Type I — laboratory findings (D.M. I). Blood sugar (by Folin technics): at least two readings on different days of more than 250 mg. per 100 cc. on venous or capillary blood or at least one post-prandial reading above 200 mg. per 100 cc. and an oral-glucose-tolerance curve rising above 200 mg. and remaining above 130 mg. at three hours, all on venous blood; and urine sugar: glycosuria of more than a trace on at least 2 specimens.

Type II — laboratory findings (D.M. II). This category includes those subjects who do not fulfill the requirements for Type I but do meet the following criteria: Blood sugar (by Folin technics): at least one reading above 170 mg. per 100 cc. (venous) and a second reading above 170 mg. on venous blood or 200 mg. on capillary blood; and urine sugar: a trace or more of glycosuria on at least two specimens.

Diagnosis (Phase III)

If a subject met the criteria described for Type I or Type II laboratory findings, he was referred for further study to his own physician or clinic. The decision concerning the precise degree of hyperglycemia and glycosuria necessary for a definite diagnosis of diabetes as well as the exclusion of other causes of hyperglycemia and glycosuria was left to the judgment of the person's physician.

The specificity of a screening procedure refers to the proportion of people selected for further testing who are truly positive. In this paper, we are comparing the specificity of blood-sugar and urine-sugar tests used in the first phase of examination as measured by the results of re-examination procedures used in the second phase. Although the patients were not given a definite diagnosis before referral to their physician, for purposes of this study we shall refer to those subjects who met the criteria for Type I or Type II laboratory findings as "newly discovered diabetics."

DESCRIPTION OF GROUP EXAMINED

Of 3186 persons on whom both blood and urine sugar tests were made, 1790 were examined as part of a community tuberculosis survey; the remaining 1396 presented themselves at the Health Department for a diabetes test. Almost all the diabetics discovered were above twenty-five years of age. Since the primary purpose of this paper is comparison of case-finding methods, the study group is limited to subjects over twenty-five years. The study group has a somewhat greater concentration of persons between forty-five and sixty-four years of age than has Brookline as a whole. In the study

*This study is based on data obtained by the co-operative efforts of residents of the town of Brookline, Massachusetts, serving as a lay advisory committee, physicians in Brookline acting as a technical advisory committee, and the Brookline Health Department (Dr. Alfred Frechette, director of public health).

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group 61.7 per cent of those tested were female, whereas in Brookline as a whole the population is 57.8 per cent female. The individuals in this series are considered sufficiently representative of the Brookline population for a study of case-finding methods. However, it would not be justifiable to use the data on these 3186 persons to estimate the prevalence of diabetes in Brookline. Although we have excluded from this study all persons who were previously known to have diabetes, there were certain factors of self-selection (such as age, previous glycosuria, diabetes in the family, symptoms) in operation during part of the study that preclude an estimate of prevalence from these data.

Detailed Clinic Procedures

Screening Procedure (Phase I)

The majority of subjects presented themselves for the initial test with no preparatory instructions except those available in local publications. A short history, taken by the nurse, included estimation of food consumed during the previous four to six hours. Time since eating was arbitrarily recorded from the beginning of the last meal containing 25 or more gm. of carbohydrate. Real efforts were made through interviews conducted by nurses to exclude those persons previously considered by their physicians to have diabetes.

Blood-sugar screening. A capillary-blood specimen was taken and analyzed by the Folin–Malmros method.[1]

From the observed blood-sugar readings of the group examined early in the series, preliminary screening levels were chosen and persons with readings above these levels were asked to return for re-examination. Since it was practical to examine subjects whenever they came to the clinic, screening levels were chosen for each time interval to select the upper 10 per cent of blood-sugar readings. The minimum screening levels that were used consistently throughout the series are as follows:

Hours After Eating	"10 Per Cent" Blood-Sugar Screening Level
	mg./100 cc.
½–1½	160
1½–2½	150
2½–3½	140
3½+	130

Urine-sugar screening. Immediately after the initial blood specimen was taken, a urine specimen was collected. It was promptly analyzed by a bismuth-oxychloride powder (Galatest). The bismuth-oxychloride urine-sugar test proved in preliminary testing to be as sensitive to urinary glucose as the standard Benedict procedure. Since it is quite difficult to distinguish between shades of gray and black (a positive test with bismuth-oxychloride), the standard Benedict procedure was used on positive and questionable tests so that some quantitative estimate could be made.[2] There were so few discrepancies between the two methods that for purposes of this study urines have been tabulated as positive or negative according to the bismuth-oxychloride test.

During the total series, all persons with definite glycosuria (more than a trace) were asked to return for re-examination. Among the first 2500 of the series, subjects were asked to return because of any degree of glycosuria, including a trace. The group with a trace of glycosuria as the only finding was large, and re-examination proved unproductive. In the latter part of the series, persons with this finding were not asked to return.

Re-examination Procedure (Phase II)

Subjects screened out were instructed to come to the Health Department for a re-examination from half an hour to one and a half hours after a high-carbohydrate meal. At that time both capillary and venous blood specimens were taken and each was analyzed by Folin[1, 3] and Somogyi–Nelson[4–6] methods. Urine-sugar determinations were made by both the bismuth-oxychloride method and the Benedict method.

If all values were obviously normal and consistent with each other at repeat examination, the investigation was carried no further. If the values on both the original test and the recheck test were sufficient to meet certain criteria defined previously, the person was then referred to his physician. If values were still high but not conclusive, the person was asked to return for an oral glucose-tolerance test. For this test, a fasting blood sugar was obtained and venous blood-sugar specimens were taken at one half, one, two, and three hours after the ingestion of 100 gm. of glucose. These tests were analyzed by the Folin-Wu and Somogyi-Nelson methods. A urine specimen was obtained when each blood specimen was taken and analyzed by the Benedict and bismuth-oxychloride methods.

Results of Screening Procedures Used

Of the 3186 persons on whom both blood and urine sugar tests were made, 338, or 10.6 per cent, had blood-sugar readings above the minimum screening levels. The percentage of subjects with readings above a given level (as 160 mg. per 100 cc.) decreased at later intervals after eating (Table 1).

It should be noted that the percentage of the group screened out varies greatly with the age of the person tested. For example, 7.6 per cent of those from 25 to 44 years of age had readings above 160 mg. per 100 cc. at the first interval, whereas 12.2 per cent of those over 45 years had readings above this point.

Of the 3186 subjects examined, 451, or 14.1 per cent, had positive urinalyses. Of the group examined, 10.1 per cent had trace reactions and 4 per cent had definite glycosuria (Table 2). The incidence of glycosuria did not vary significantly in relation to time after eating. Furthermore, the incidence of

glycosuria was remarkably consistent for the different age groups examined.

Since blood-sugar and urine-sugar tests were essentially simultaneous, the related urine and blood-sugar results are of interest. If all subjects with blood-sugar readings above the minimum screening levels and all with glycosuria were screened out for further testing, 695, or 21.8 per cent of the total, would be included. Only 95 persons were "positive" on both tests, whereas 244 were "positive" on the blood-sugar test alone and 356 were "positive" on the urine-sugar test alone. It is apparent that either test used singly would not have screened out the same group for re-examination (Table 3).

TABLE 1. *Capillary Folin-Malmros Blood-Sugar Readings of 3186 Subjects Over 25 Years of Age: Percentage Above Given Levels by Hours after Eating.*

Capillary Folin-Malmros Blood-Sugar Levels	½ to 1½ Hours after Eating	1½ to 2½ Hours after Eating	2½ to 3½ Hours after Eating	3½ (or More) Hours after Eating
mg./100 cc.				
130 and above				9.9
140 and above			9.2	5.5
150 and above		12.1	5.2	2.3
160 and above	10.1	7.2	2.7	1.4
170 and above	7.1	4.4	2.2	0.9
180 and above	5.3	3.3	1.8	0.5
190 and above	3.6	2.5	1.3	0.5
200 and above	2.6	1.8	1.3	0.5
Number examined	1191	1116	446	433

Completeness of Follow-up

In Table 3 the completeness of follow-up for different types of laboratory results is shown. It is apparent that greater success in follow-up was obtained in persons with the more significant blood-sugar and urine-sugar findings, especially for those in whom both tests were positive. This was due in part to some variation in effort on the part of the nurses, — since this was a case-finding program, — and also to inevitable self-selection on the part of patients who had symptoms or other cause for unusual interest.

It became apparent after 2500 subjects had been tested that further re-examination of individuals with a trace of glycosuria as the only finding would be definitely unprofitable. Only one case of diabetes was discovered by re-examining 139 persons with a trace, or 0.7 per cent, of glycosuria as the only finding (Table 3). Accordingly, 66 of those who showed a trace of glycosuria as the only finding were not requested to return during the latter part of the study. This accounts for the lower follow-up rates for those subjects with a trace of glycosuria. Of those with a trace of glycosuria who were requested to return for re-examination, 70 per cent follow-up was possible. Based on numbers actually asked to return, the percentage of follow-up of all subjects with glycosuria would be 75.8, which is comparable to the 74.9 per cent follow-up of positive blood-sugar readings.

General Case-Finding Results

In the group of 3186 persons examined, 71 newly discovered diabetics were found, using the procedures and classifications described above. Of these, 38 were men and 33 women. Of the diabetics, 12 were under 45 years of age, 38 were between 45 and 64 years and 21 were over 65 years of age.

Of these 71 new diabetics, 43 had Type I laboratory findings and 28 had Type II findings. Those diabetics classified as Type I did not differ from those classified as Type II in age distribution.

Comparison of Specificity and Sensitivity of Urine-Sugar and Blood-Sugar Screening Procedures

In establishing a screening procedure two important factors must be weighed against each other:

What proportion of the truly positive subjects in the total population will be found (sensitivity of the test)?

What proportion of those singled out for further testing are truly positive (specificity of the test)?

General Technic Used for Comparison

A screening test that measures a substance, such as "sugar," that is normally present in varying degrees in the blood presents certain problems in evaluation. By setting the blood-sugar level to be used as a screening test low enough, one could ensure 100 per cent sensitivity. To do this, however, would make the specificity of the test very low, since a great amount of unnecessary follow-up work would be involved. If the levels are set high enough 100 per cent specificity can be obtained, but the test becomes low in terms of sensitivity. A similar flexibility in setting screening levels does not obtain in urine-sugar screening tests. For practical purposes there is little value in quantitating positive tests in more than two categories, in view of the dilution variables that exist when single specimens are used. These categories are: "trace" reactions and definite glycosuria of more than a "trace." The urine-sugar screening test can be judged in terms of its specificity or sensitivity at these two levels. For this comparison, levels for blood-sugar screening were chosen to correspond with the group screened out for re-examination because of definite glycosuria.

TABLE 2. *Results of Urinalyses in 3186 Subjects Over 25 Years of Age.*

	No. of Subjects	Percentage of Total Examined
Total urinalyses	3186	100.0
Positive	451	14.1
Positive — trace glycosuria	322	10.1
Positive — more than trace glycosuria	129	4.0

The data available from this study can readily be used for a comparison of the specificity of blood-

sugar and urine-sugar screening tests. However, certain variables must be fixed for both tests in question. We have chosen to compare the screening tests using criteria in each case that will single out roughly the same number of people to be re-examined. Those subjects with more than a trace of glycosuria on initial examination represented 4 per cent of the 3186 examined. In retrospect, blood-sugar screening levels that would also select approximately 4 per cent for re-examination were set up for comparison with urine-sugar screening. The levels above which 4.3 per cent of the total examined fell are as follows:

Hours After Eating	"4 Per Cent" Blood-Sugar Screening Level
	mg./100 cc.
½–1½	180
1½–2½	180
2½–3½	160
3½+	140

It is necessary to assume that the diabetics in the groups selected for further testing by each method have subsequently all been detected or have been detected in equal proportion in each of the two groups. To make this assumption, relatively complete follow-up must have been accomplished in both groups. Of the group with definite glycosuria, 86.8 percent were successfully followed and re-examined. Of the 135 subjects with blood-sugar readings above the "4 per cent" screening levels, 86.7 per cent were rexamined. Thus two groups — those with glycosuria of more than a trace and those with blood-sugar readings above the "4 per cent" screening levels — form the basis for the comparison below.

Specificity

As a measure of the specificity of the two tests we are comparing the percentage of re-examined "positives" who were found to have diabetes (Table 4). Of 112 persons re-examined because of definite glycosuria on initial examination, 40 were found to have diabetes (35.7 per cent). Of 118 subjects re-examined because of blood-sugar readings above the "4 per cent" screening levels, 58, or 49.2 per cent, were classified as diabetic. The difference between 49.2 and 35.7 per cent may be expected to occur by chance alone less than 5 times in 100, if there were no real difference in the specificity of the two tests.

If one divides the diabetics discovered into Type I and Type II, it becomes apparent that the greater specificity of blood-sugar tests lies in the discovery of persons with less marked hyperglycemia and glycosuria. Of subjects examined because of positive urines, 30.4 per cent showed Type I findings. Of those examined because of "positive" blood-sugar readings 32.2 per cent showed Type I findings. The difference between these rates may well be attributed to chance. On the basis of urine-sugar tests, 6 Type II new diabetics were found, — or a percentage of 5.4. On the basis of blood-sugar tests, 20 Type II new diabetics were found, a percentage of 16.9. The difference between 16.9 and 5.4 per cent may be expected to occur by chance alone less than one time in 100, if there were no real differences in the specificity of the two tests.

TABLE 3. *Results of Screening 3186 Subjects by Related Urine and Blood-Sugar Findings, Using "10 Per Cent" Screening Levels.**

		Subjects Tested	Subjects Retested		Subjects Found to Be Diabetic	
		no.	no.	*percentage with positive tests*	no.	*percentage of number retested*
Total positive findings*		695	460	66.2	71	15.4
Total positive urine sugar		451	292	64.7	47	16.1
Total positive blood sugar		339	254	74.9	67	26.4
Urine	*Blood*					
I. Positive	Positive	95	86	90.5	43	50.0
A Trace	Positive	45	41	91.1	6	14.6
B Trace +	Positive	50	45	90.0	37	82.2
II. Positive	Negative	356	206	57.9	4	1.9
A Trace	Negative	277	139	50.2	1	0.7
B Trace +	Negative	79	67	84.8	3	4.5
III. Negative	Positive	244	168	68.9	24	14.3

*Subjects with blood-sugar readings above the "10 per cent" screening levels or with glycosuria of a trace or more, or both, are classified (as indicated in the text) as "positive."

Sensitivity

A strict comparison of the sensitivity of blood-sugar and urine-sugar tests is not possible from the data collected in this study. To measure sensitivity of the tests would require a knowledge of the exact number of diabetics in the total population screened (3186 persons), using some technic that was independent of the tests in question. No such test is available at the present time. Re-examination of all the negatives or a large enough sample of the negatives might have provided such a measure, but this was not practical in this community case-finding program.

We can, however, make some inferences as to the relative sensitivity of the blood-sugar and urine-sugar screening technics if we assume that the 71 new diabetics found by all methods used in this case-finding program represent at least the bulk of the previously unknown diabetics in this group of

3186 persons. We can see how many of these diabetics would have been found if either the blood-sugar or urine-sugar screening tests had been used alone to single out equal numbers of persons for further study.

If only the urine-sugar test had been used as a case-finding method, with those subjects with more than a trace of glycosuria returning for re-examination, 40, or 56.3 per cent, of the 71 new diabetics would have been found. If only the blood-sugar test had been used, screening with the 4 per cent screening levels, 58 of the 71 new diabetics would have been found, — or 81.7 per cent.

By using a combination of the blood-sugar and urine-sugar screening technics at the 4 per cent levels, 62 of the 71 new diabetics would have been found. Of these 62 new diabetics, 36 were positive on both tests, 4 were positive only on urine tests and 22 were positive only on blood tests. Of the 22 new diabetics who were positive only on the blood-sugar screening test, 16 had laboratory findings of Type II.

From the above we may infer that the blood-sugar screening test was more sensitive than the urine-sugar screening test when equal numbers of subjects were brought back for further testing by each procedure. The increased sensitivity of the blood-sugar test was apparently due to its greater ability to detect those persons with the milder type of laboratory findings (Type II).

Consideration of Alternate Blood-Sugar Screening Levels

A procedure set up to re-examine approximately equal numbers of positive blood-sugar and urine-sugar tests has been discussed. However, it is not necessarily true that these are the optimum screening levels if either test is used singly. The relative efficiency of screening at alternate blood-sugar levels may be seen by examination of Table 5.

It is apparent that as screening levels are lowered more people will have to be re-examined to find progressively fewer diabetics. Judgment concerning the lowest practical screening point would depend on desired completeness of case-finding and facilities for re-examination. For example, through the use of the 10 per cent screening levels in this case-finding program, rather than the 4 per cent screening levels which we have set up in retrospect, 136 additional people were re-examined to find 9 additional diabetics.

Consideration of Alternate Urine-Sugar Screening Technics

An important problem in screening with urine-sugar determinations alone is whether or not to recheck all "trace" reactions (gray color with bismuth-oxychloride or blue-green to green with Benedict solution). Since 10.1 per cent of the Brookline series showed trace reactions and only 4 per cent showed more than a "trace" (a total of 14.1 per

Table 4. *Results of Screening 3186 Subjects by Related Urine and Blood-Sugar Findings, Using "4 Per Cent" Screening Levels.**

		Subjects Tested	Subjects Retested		Subjects Found to Be Diabetic	
		no.	no.	*percentage with positive tests*	no.	*percentage of number retested*
Total positive findings		223	192	86.1	62	32.3
Total positive urine sugar		129	112	86.8	40	35.7
Total positive blood sugar		136	118	86.7	58	49.2
Urine	*Blood*					
Positive	Positive	42	38	90.5	36	94.7
Positive	Negative	87	74	85.1	4	5.4
Negative	Positive	94	80	85.1	22	27.5

*Subjects with more than trace of glycosuria are classified as "positive." Individuals with blood-sugar readings above the levels indicated in the text are classified as "positive."

Table 5. *Results of Screening at Given Blood-Sugar Levels by Intervals after Eating.*

Capillary Folin-Malmros Blood-Sugar Levels	½-1½ Hours after Eating				1½-2½ Hours after Eating			
	no. above level	no. retested	Subjects found to be diabetic		no. above level	no. retested	Subjects found to be diabetic	
mg. /100 cc.			no.	*percentage of number retested*			no.	*percentage of number retested*
150 and above					135	94	28	29.8
160 and above	120	96	23	24.0	80	66	26	39.4
170 and above	85	75	21	28.0	49	42	24	57.1
180 and above	63	57	21	36.8	37	33	23	69.7
190 and above	43	41	18	43.9	28	27	21	77.8
200 and above	31	30	15	50.0	20	19	17	89.5
Number examined	1191				1116			

cent with positive urines) it is apparent that this decision will be very important in determining the amount of repeat testing necessary. From examination of these data we have not been able to find any criteria by which the trace reactors could be divided into a productive and an unproductive group without knowing their blood-sugar readings. We were unable to single out any group on the basis of age or of time after eating for which the follow-up of trace reactions was particularly productive.

If the blood-sugar reading is known the decision becomes quite simple. Of 41 persons rechecked because of a trace of glycosuria and a blood-sugar value above the 10 per cent screening level, 6, or 14.6 per cent, eventually met the criteria for "new diabetics." Of those rechecked because of a trace of glycosuria as the only finding (139), only one met the criteria for "new diabetics." The results of re-examining urine-sugar findings by related blood-sugar results are shown in Table 3.

Discussion

In evaluating these data certain facts should be kept in mind. We were interested in obtaining information on blood-sugar and urine-sugar screening tests for diabetes under the conditions that exist during actual field operations. The laboratory results were frequently checked, and we believe this work was of good quality. It was a routine laboratory, however, in the sense that work came in showers of activity and pressure. The collection of samples had to be done in a simple fashion, taking a minimum of the patient's time. There was no standard previous meal. A single urine specimen was obtained at the time that the patient presented himself; "second specimens" were not taken to minimize dilution variables. These are, however, the conditions that usually exist in a practical case-finding program and that frequently exist when specimens are taken in a physician's office. We do not know how much the efficiency of urine-sugar determinations could be improved by controlling some of these factors.

Testing these screening tools on a series of known diabetics under research conditions would give information that would be valuable but of a different kind. The diabetics in this series are of the type that goes unrecognized in the community by definition; hence they offer no problem of selection. No one knew at the time that the tests were made which were the large group of "normals" and which the "diabetics."

We were somewhat surprised at the lack of correlation that existed between the specificity of urine-sugar testing and various hours after eating. We do know, however, from experience with glucose-tolerance tests in this group of diabetics, that fasting urine-sugar or blood-sugar determinations would not have brought the majority of patients to a physician's attention.

In selecting a screening procedure, one must decide in a given situation the point at which it is not worth the effort and expense to find additional cases. It is clear to us that if one is interested in finding mild degrees of hyperglycemia and glycosuria, blood-sugar screening is definitely more efficient than urine-sugar screening when the same number of people are singled out by each test for further study. The difference between the two procedures, however, is much less marked if one is only interested in finding those with more marked hyperglycemia and glycosuria.

From the point of field practice, there was little difference in the difficulties in collecting urine and capillary-blood specimens. With technics available for simple blood-sugar determinations,[7] the cost of laboratory procedures should be about the same in either case.

Summary and Conclusions

Data have been presented to show the relative specificity and efficiency of urine-sugar and blood-sugar determinations as screening procedures for diabetes.

Of 3186 persons over 25 years of age examined in Brookline, Massachusetts, 71 "newly discovered diabetics" were found by using both blood-sugar and urine-sugar determinations as the initial screening procedure.

If only those subjects with more than a trace of glycosuria (4 per cent of the total group) had been re-examined, 40 of the 71 cases would have been found.

If only those subjects with blood-sugar readings above the levels that screened out 4 per cent of the group had been re-examined, 58 of the 71 cases would have been discovered.

By re-examining approximately the same number of persons (4 per cent of the total group) on the basis of the urine-sugar screening test and the blood-sugar screening test, it is possible to compare the specificity of the two tests. Of those singled out for re-examination by the urine-sugar test, 35.7 per cent were "new diabetics." Of those singled out for re-examination on the basis of the blood-sugar examination, 49.2 per cent were "new diabetics."

If the "new diabetics" found are divided into two groups according to the severity of their laboratory findings, it becomes evident that the greater efficiency of blood-sugar screening is shown principally in the location of those subjects with less marked hyperglycemia and glycosuria on re-examination.

Data have been so presented that some prediction can be made of the work involved and the productivity to be expected in the utilization of either procedure.

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THE RELATION OF SEX, PREGNANCY AND MENSTRUATION TO SUSCEPTIBILITY IN POLIOMYELITIS*

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MANY of the general features of the distribution of poliomyelitis are reflections of the widespread dissemination of the virus as it is affected by immunity in the population resulting from previous exposure. Within this broader pattern of distribution there are further restrictions and selectivities in the occurrence of the frank disease that are indicative of the operation of other factors of susceptibility or resistance. Among the many who are exposed to the virus, the preponderant result of which is subclinical immunization, the more frequent occurrence of frank poliomyelitis under particular circumstances and in particular categories of individuals affords some indication of the nature of the mechanisms of susceptibility that are involved.

Variations in the frequency of the clinical infection, apparent and inapparent, in relation to climate and season suggest that corresponding variations in physiologic functions, — possibly some fault in adaptation to changing environment, — may play an important role.[1] The greater incidence of poliomyelitis in patients of a distinctive constitutional type has been interpreted as an indication of an inherent ability in such persons to develop clinical manifestations on contact with the virus.[2, 3] Evidence of familial tendency to the frank disease suggests that such a mechanism of susceptibility may, at least in part, be transmitted by inheritance.[4] The occurrence of bulbar poliomyelitis after tonsillectomy appears to represent a localized breakdown in the normal defense mechanism.[5-10] The frequent occurrence of poliomyelitis during pregnancy points to a temporary state of susceptibility doubtless associated with some physiologic change incident to the gravid state.[11-13] In addition to these more definitive selectivities in the occurrence of frank poliomyelitis, the effects of other circumstances preceding the onset of the infection, such as overexertion and fatigue, are a matter of common clinical observation. The relation here is less clearly defined, perhaps because of difficulties in precisely defining or timing such events in relation to the onset of the disease. Recently, injection of pertussis vaccine and diphtheria toxoid has been related in point of time to the development of paralysis as well as to its localization.[14-18] The restriction of such instances to epidemics of poliomyelitis, in which inapparent infections are known to occur in considerable excess of clinically recognizable ones, is enough to suggest that they do not result from contaminated material or syringe infection but represent detonation of subclinical into clinical disease.

It is not known whether the mechanisms of susceptibility that are involved in these exceptional selective occurrences of poliomyelitis are aberrant and unrelated or whether they all affect, in different ways, the same basic mechanism of defense that is disturbed in an as yet unknown manner in the majority of cases and that is doubtless responsible for the extraordinarily high resistance of man to the development of clinical disease. That the latter may be the case has been suggested by a consideration of a number of these selectivities, from which was derived the hypothesis that their common denominator might reside in the economy of some of the sex hormones.[19] This idea is supported by the enhancement of resistance to the experimentally produced disease by preparatory administration of estrogenic materials[19] and by the production of active immunity without disease by the inoculation of animals with fully active virus while maintaining them under the protection of estrogens.[20] That these experimental findings may reflect conditions that play a role in the human disease is suggested by the finding of differences in levels of secretion of estrogenic hormones and 17-ketosteroids in patients with poliomyelitis and in healthy controls.[19, 21]

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In view of the accumulating evidence that factors residing in the exposed person, in addition to factors of exposure, may play an important role in the pathogenesis of clinical poliomyelitis, certain observations on the occurrence of poliomyelitis during pregnancy and the possible relation of sex and of menstruation to susceptibility to this disease are reported in this paper.

Epidemiologic Observations

During the year 1949, 1770 cases of poliomyelitis were reported in Massachusetts, 416 being admitted to the Haynes Memorial Hospital in Boston. Of the 82 female patients between 20 and 40 years of age in the hospital, 20, or approximately 25 per cent, were pregnant. During 1950, 485 cases were reported in the state; of 134 studied at the Haynes Memorial, 6, or 23 per cent, of 26 females, aged 20 to 40, were pregnant. As estimated from rates of living and still births, approximately 7 per cent of all women in this age group would be pregnant at a given time. Thus, of the 108 women of these ages admitted to the hospital during the two-year period there should not have been more than 10 who were pregnant. Tables 1 and 2 present the

Table 1. *Age, Sex and Pregnancy in Poliomyelitis (1949).*

Age	Massachusetts		Haynes Memorial			
	Male	Female	Male	Female	Pregnant	
					Expected	*Observed*
0–4	212	142	22	16		
5–9	264	181	38	34		
10–14	228	118	57	27		
15–19	110	75	33	26	0.9	0
20–24	76	70	32	22	2.3	6
25–29	63	88	23	33	2.8	9
30–34	32	47	15	23	1.5	4
35–39	19	21	6	4	0.2	1
40–44	4	10	0	3	0.1	0
45–49	3	4	1	0		
50 and over	2	1	1	0		
Totals	1013	757	228	188	7.8	20

age and sex distribution of cases hospitalized in 1949 and 1950 and the expected and observed incidence of pregnancy. It is notable that the number of pregnant women was 3 times greater than would have been expected by coincidence. This figure is in close agreement with numerous other reports on the frequency of poliomyelitis during pregnancy.

Tables 1 and 2 also show that in patients hospitalized with poliomyelitis, males were in considerable excess over females in the younger age groups whereas in the adults there was a shift to a preponderance of females. However, before these statistics can be interpreted as indicating an actual increase in the occurrence of the disease in pregnant women, it should be ascertained whether patients were sent to the hospital more frequently because of the complicating circumstance of pregnancy. Figure 1 shows a similar shift to females in the older age groups in cases reported in the state as a whole. From this it is evident that the hospital admissions reflect the actual sex distribution and not simply an increase in hospitalization because of pregnancy. It should be stated that the difference in age between the patients in the hospital and those reported in the state as a whole is the result of the admission of a larger proportion of younger persons to institutions other than the one in which the study was carried out. Data are not available concerning the frequency of poliomyelitis in pregnancy in

Table 2. *Age, Sex and Pregnancy in Poliomyelitis (1950).*

Age	Massachusetts		Haynes Memorial			
	Male	Female	Male	Female	Pregnant	
					Expected	*Observed*
0–4	50	38	6	3		
5–9	83	54	19	13		
10–14	51	36	13	9		
15–19	28	16	14	7	0.2	0
20–24	17	17	4	9	0.9	3
25–29	20	26	5	9	0.8	1
30–34	11	12	6	6	0.4	2
35–39	4	9	3	2	0.1	0
40–44	2	4	2	2	0.1	0
45–49	3	1	0	1		
50 and over	1	2	1	0		
Totals	270	215	73	61	2.5	6

Massachusetts at large, although information from various sources indicates that there were more cases than would have been expected by coincidence.

It is clear that a part of the greater incidence of poliomyelitis in women in the older age groups can be accounted for by an increased occurrence of the disease in pregnancy. However, if the pregnant patients are taken out of the hospital series, there is still a small preponderance of females in the adult group. The disproportion in the number of cases in the two sexes could be due to a corresponding difference in sex ratio of the population or to variation in exposure to the virus or in susceptibility to clinical disease in the two sexes at different ages. Census figures do not show a corresponding sex difference in the composition of the population in Massachusetts or in the country as a whole.

The pattern of distribution of antibodies to poliomyelitis virus, both for monkey-adapted and the mouse-adapted Lansing strain, is, in general, similar to those of diphtheria and scarlet fever as shown by Schick and Dick tests. These end-point measurements are indicative of a similar widespread dissemination of the three infectious agents, resulting predominantly in inapparent immunizing infection and only exceptionally in clinical disease. In diseases such as rubeola, mumps, varicella and pertussis, for which no practical test for immunity is available, the incidence at different ages suggests that the patterns of infection and population immunity are the same. In none of these indices are there any indications of differences in exposure that could account for a sex ratio of clinical cases such as that observed in poliomyelitis. In the widespread immunizing infections as a group (measles, mumps,

scarlet fever, whooping cough and diphtheria) the sex ratio of cases is approximately equal in the younger age groups, but there is, as is well known, an excess incidence in older females over that in males. This is attributed to increased opportunity of household exposure in adult women. In none of these is there a shift in the sex distribution, however, of the order of that noted in poliomyelitis. Turner and others[22] have shown that the pattern

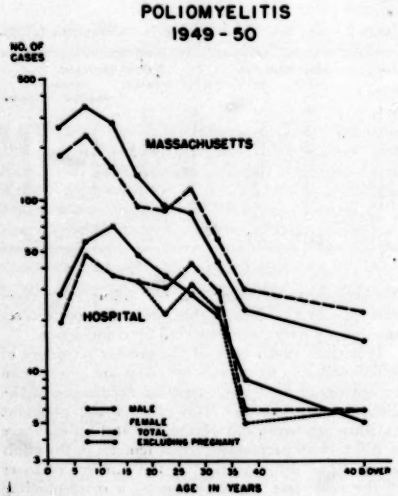

FIGURE 1.

of immunity to the Lansing strain of virus, from the point of view of age, is the same in both sexes. It is for these reasons that the upswing in the ratio of female to male cases beyond that which can be accounted for by the increased occurrence of this infection in pregnant women raises the possibility that there may be still another mechanism of susceptibility to clinical disease that is peculiar to the adult female. Because of the implications of pregnancy and of other selectivities that suggest a hormonal mechanism as a possible factor, it was decided, after the experience in 1949, to ascertain whether or not there was any relation between the menstrual cycle and the occurrence of clinical poliomyelitis.

Clinical Observations

A group of 50 women, admitted to the Haynes Memorial Hospital with poliomyelitis in 1950, were questioned carefully concerning the onset of menstruation in relation to the appearance of the first symptoms of their illness. Since a great many of them were still menstruating when admitted to the hospital it was possible to date the onset of the flow accurately. From the data presented in Figure 2 it can be seen that 78 per cent of the patients had a menstrual period from five days before to four days after the beginning of illness. Although other cases showed no such correlation, they were distinctly in the minority. Quite striking is the fact that of those in whom poliomyelitis appeared in close temporal relation to the menses there were almost twice as many in whom the flow started within the first four days *after* the appearance of symptoms than there were in whom menstruation

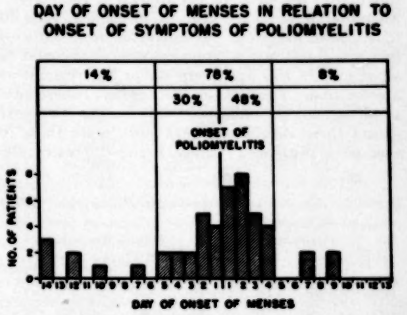

FIGURE 2.

began within 5 days *prior* to the onset of clinical manifestations of disease. The frequent correlation of menstruation with the first appearance of symptoms and signs of poliomyelitis is very striking and suggests the possible importance of endocrine factors in provoking or hastening central-nervous-system invasion. The relation, as shown, was not due to change in the usual length of the intermenstrual interval, since none of the patients gave a history of early or delayed onset of the period that occurred near the time of onset of poliomyelitis. In order to rule out, as much as possible, the chance that this frequent association was not merely coincidental, the records of 365 females between the ages of 15 and 45 who had been admitted to the Haynes Memorial Hospital for a variety of diseases other than poliomyelitis were examined with respect to a temporal relation between the onset of illness and menstruation. Of this group 61, or 16.7 per cent, had a menstrual flow at the time of admission or within three to four days after. When the patients were separated into groups on the basis of the presence or absence of an infectious disease it was found that 17.9 per cent of 240 women with

infection and 14.4 per cent of 125 with noninfectious diseases were menstruating. When these are compared with the patients who had poliomyelitis it can be seen that menstruation was present about 4.5 to 5.5 times more frequently in those with the nervous-system disease than in those who had other types of illness. Although the group reported in this paper is too small to permit any absolute conclusions concerning a definite correlation between the phase of the menstrual cycle and the onset of poliomyelitis, the observations that have been made are highly suggestive of such a relation, and the question merits further investigation.

Discussion

The data presented above clearly indicate the effect of pregnancy in increasing susceptibility to clinical poliomyelitis and confirm the observations previously recorded in the literature stressing this relation. The exact role that the gravid state plays and the part of the disease on which it exerts its influence are unknown at this time. The important endocrinologic changes that accompany pregnancy suggest themselves immediately as possible causal factors, but whether it is the hormones excreted by the pituitary or those elaborated by the placenta or even the cessation of activity of the ovaries that is responsible for this phenomenon cannot be determined. Changes in function of other than the sex-hormone-elaborating tissues, for that matter, may be responsible, since the activity of the thyroid, adrenal and other endocrine glands may be markedly altered during pregnancy. The particular phase of the infection that is affected by the pregnant state is a matter for speculation only. Two possibilities exist: that the host is made more susceptible to initial invasion by the virus, and that the woman harboring virus without showing clinical evidence of disease is rendered highly susceptible to invasion of the nervous system.

In addition to increasing susceptibility to poliomyelitis, pregnancy may also alter the course of the infection after it is already present. Women who develop the disease early in pregnancy and are well along in the convalescent phase at the time of delivery suffer no ill effects. If, on the other hand, parturition takes place in the acute phase or shortly thereafter, we have frequently observed an increase in severity of the paralysis or extension of involvement to muscles previously unaffected. The mechanisms involved in these changes are not known, although it might be speculated that the rather sudden hormonal changes that occur after delivery may alter the susceptibility of the nervous-system tissues to damage by virus; if this is so, however, then the same effect must be produced on the nervous system by two distinctly opposite types of endocrine situations, namely, pregnancy and the post-partum state. The possibility that the physical exertion associated with the process of labor may be responsible for the increase in severity of the infection must also be considered.

The possible role of the sex hormones in the pathogenesis of clinical poliomyelitis is supported by the observation that certain phases of the menstrual cycle may be correlated with increased susceptibility to the development of nervous-system involvement. The spread of onset of the disease around the day of beginning menstruation is not unlike that resulting from variation in the incubation period of the disease. This suggests the possibility that there may be a critical point in the menstrual cycle in respect to susceptibility to clinical poliomyelitis at an interval corresponding to the incubation period preceding the beginning of menstruation — or about twelve days prior to the onset of the menstrual flow.

Conclusions

Pregnancy increases susceptibility to poliomyelitis.

Parturition in the acute phase of poliomyelitis increases the risk of extension of paralytic manifestations.

Taking pregnant patients into consideration, there is still a preponderance of females with poliomyelitis in the adult group.

About three fourths of women patients with poliomyelitis have a menstrual period from five days before to four days after the onset of the first symptoms of this infection. This observation requires more intensive study.

The apparent role of sex, pregnancy and menstruation in increasing susceptibility to poliomyelitis in the adult re-emphasizes the possible influence of the sex hormones or other endocrine substances on the pathogenesis of this disease.

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THE INFLUENCE OF POSITION ON THE BREATH SOUNDS*

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NEW ORLEANS, LOUISIANA

A SURVEY of 26 standard textbooks on physical diagnosis[1-26] reveals that in only three[15, 23, 24] is there a specific reference to the nature of the variation in breath sounds occurring with change in position. According to two of these[23, 24] the breath sounds on the dependent side are diminished, whereas the other[15] states that they are increased. The present study seems to clarify this little known, though admittedly insignificant point.

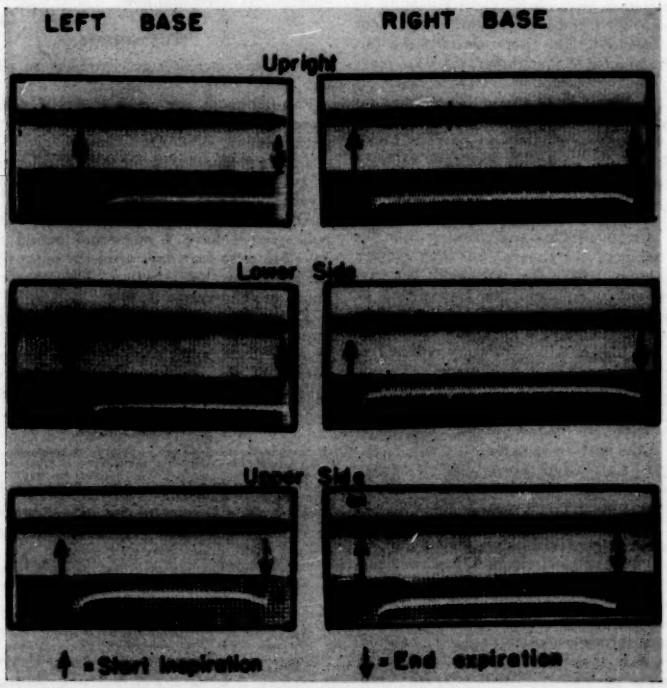

FIGURE 1. *Breath Sounds of Normal Male Subject with Changes in Posture.*

METHOD AND MATERIAL

Auscultation of the chest was performed on 58 men and women from the clinics and wards of

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Charity Hospital in New Orleans, with the subjects in the upright and both recumbent positions. Eleven of these had pulmonary disease and 8 had extremely enlarged hearts; the remainder showed no abnormalities of the heart or lungs. The patient was first examined on the left side in each instance. Patients in the clinic were examined on a hard-surfaced table, those on the ward on soft mattresses on spring beds. In several instances other examiners were asked to verify the observations.

Results

Thirty-six of the normal subjects and 7 of those with pulmonary disease, whose breath sounds were equal on both sides in the upright posture, showed, on changing position, an increase in both intensity and pitch of the inspiratory note at the base posteriorly on the dependent side. Diminution of the breath sounds on the opposite side in a comparable area was noted. In a few instances the breath sounds were almost absent over the upper base. Changes of an inconstant nature were noted in 3 normal subjects, in 4 of the 7 with pulmonary disease and in all 8 of those with enlarged hearts. Particular attention was focused on the expiratory murmur, and in only 11 of the entire 58 patients was any increase in pitch, duration or intensity noted in this phase.

A sound tracing made with a Cambridge stethocardiograph on a normal male subject is shown in Figure 1. It indicates the usual change observed on auscultation.

Discussion

The location of the diaphragm in the lateral decubitus position was studied by Howard[27] and by Adams and Pillsbury.[28] Roentgenographic studies made by Howard showed the dependent leaf of the diaphragm to be higher in the 50 patients examined. The latter authors, by roentgenographic measurements, showed the excursion of the dependent leaf to be twice as great as the upper component.

The first reference in the English literature to postural change in breath sounds was made in 1903 by Conner and Dodge.[29] They stated that the breath sounds of the dependent side have a tubular quality. Guthrie[30] described the breath sounds on the dependent side as usually having a "faint tubular element." The observations of Adams and Pillsbury are in agreement with those of Guthrie.

Comment

The results of the present study and the roentgenographic observations cited indicate greater aeration of the dependent lung in the usual patient. A "tubular quality" in the breath sounds of the dependent lung previously described by some observers could not be demonstrated in the present study. The prolonged inspiratory note may possibly suggest such a quality to the casual listener. The results of this study are in agreement with the statement of Norris and Landis[15] that the breath sounds are increased in intensity on the dependent side.

Summary and Conclusions

Variations in breath sounds with change in position were studied in 58 subjects, of whom 39 were normal, 11 had pulmonary disease and 8 had enlarged hearts.

With the subject in the lateral position an increase in pitch and intensity of the inspiratory note was usually observed on the dependent side, with a decrease in intensity of both phases on the upper side.

Auscultatory sounds other than those in the upright position should be interpreted with caution.

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MEDICAL PROGRESS

RADIOLOGY IN BONE PATHOLOGY (Concluded)*

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Pseudotumors

An intermediate group of lesions that fail to find a definite categorical "home" have been given the prefix of "pseudo-." Under this heading fall certain conditions in which diagnosis is important in order to prevent unnecessary surgery, especially amputation. Bone changes accompanying hemophilia and pseudohemophilia[89, 90] exemplify this.

In certain anemias, such as the Mediterranean types and hemolytic jaundice, extramedullary hematopoiesis with bone structure may take place in unusual areas, — heterotopic bone marrow in paraspinal areas, for instance.[91] These masses of heterotopic bone marrow are considered compensatory and are not malignant tumors. They may, however, be mistaken for such unless full clinical data are available to the radiologist.

Confusing masses of hypertrophic callus may be found,[92, 93] and conditions such as march fractures and Panner's disease may be mistaken for pseudotumors.

Miscellaneous Bone Lesions

Fibrous dysplasia. This condition, whether of single or polyostotic type, is now recognized much more frequently than in the past.[94-96] In an occasional case hemorrhage into a part of the lesion has produced a radiographic appearance that simulated malignant tumor.[97] It now seems likely that the condition formerly called leontiasis ossea can frequently be explained as fibrous dysplasia.[98-100] Fibro-osteoma and ossifying fibroma, particularly when located in the cranial skeleton, have been described as being related to the embryonal development of membranous bone.[101, 102] Majority opinion, however, holds that these entities are manifestations of fibrous dysplasia.

Tuberous sclerosis is generally regarded as a tissue dysplasia of ectodermal origin, although defective development and tumor formation may be identified elsewhere. At x-ray examination, in addition to the small multiple intracranial calcifications, bone changes including sclerosis, periosteal thickening, rarefaction and cyst formation may be evident. Common sites are the hands, metatarsals and skull.[103-105]

Osseous changes in sickle-cell anemia have been extensively discussed.[106-109] In this condition the bone abnormalities are due to two factors: hyperplasia of the marrow and thrombosis, which results in infarction and regeneration of bone. In adults there is generalized bone sclerosis and occasional thickening of the cortex and periosteal reaction. Disturbances of growth take place in children, but the predominant change is widening of the medullary cavity, in contrast to the marked narrowing seen in adults, and irregular trabeculation of bones due to the loss of finer markings. Hyperplastic changes result in softening of bone and enlargement of the intervertebral disks into the vertebral bodies. Infarction of bone is usually without symptoms, except when it occurs around a joint. In the growing child the development of arthritic changes about the hip is common, probably representing a combination of softening of bone and infarction of the femoral head. The aseptic necrosis associated with sickle-cell anemia may simulate osteomyelitis, particularly in children. Histologically and roentgenologically, bone infarction presents a similar appearance, regardless of its etiology. On the roentgenogram, initial zones of decreased density may be seen to proceed to complete reossification or to persist and become surrounded by linear areas of sclerosis, — or the entire necrotic area may become densely calcified. Classical bone infarction has been described in caisson disease.[110]

The occurrence of aseptic necrosis of the metatarsal head in adults (Panner's disease)[111] is of some interest. Its causative mechanism is apparently similar to that of march fracture. Healing is slow, and there is residual deformity of the metatarsal head.

Myeloid metaplasia is a well recognized clinical and pathologic syndrome of varying etiology that, according to Block and Jacobson, [112] is characterized by the constant occurrence of extramedullary hematopoiesis in the spleen and liver. It is divided into two general types, a primary type with no known etiology and a secondary type that occurs in lesions of the bone marrow such as metastatic carcinoma, marble bones, and myelofibrosis or osteosclerosis. In the secondary type particularly bone abnormalities can be observed that are suggestive but not characteristic of this condition. Secondary myelofibrosis has been noted in Paget's disease, myeloma, metastatic carcinoma (particularly from the pros-

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tate), septicemia, benzene and radiation poisoning, the various granulomatoses and polycythemia. In a single case report of secondary myelofibrosis associated with prostatic carcinoma[113] the entire skeleton was involved. It is suggested that as a result of metaplasia of the yellow marrow into red marrow, sites not ordinarily affected (the hands and feet) became fertile soil for the implantation of metastatic foci.

Sussman[114] reports 9 cases of myelosclerosis and describes the roentgenographic appearance of the bones, all of which except the skull were involved. At first the trabeculae become wider and denser than normal; this is followed by deposition of bone in an irregular fashion through the marrow so that the entire medullary cavity becomes dense and the endosteum merges into the marrow. No periosteal reaction is evident.

Reviewing bone sclerosis associated with leukemia and in nonleukemic myelosis, Windholz and Foster[115] stress certain practical points: Roentgenographic signs of bone sclerosis should arouse suspicion of leukemia; monostotic and polyostotic sclerosis occur often in monocytic leukemia and in the aleukemic lymphadenoses; panostotic sclerosis is more characteristic of nonleukemic myelosis than of lymphatic leukemia.

Eosinophilic granuloma. This granulomatous process was described as a disease entity in 1940 by Jaffe and Lichtenstein and was elaborated in 1944.[116] It has been reported as appearing in most of the bones of the body[117-119] and, according to a recent report,[120] in soft tissue. Many investigators have advanced the belief that eosinophilic granuloma, Hand-Schüller-Christian's disease and Letterer-Siwe's disease are merely different phases of the same process.[121-122]

Osteitis pubis, described in 1924 by Baer, has a varied etiology.[124-128] It occurs most commonly after prostatectomy (a few days to several months); pain is the striking symptom; recovery is slow. The bones show roughening or fraying of the periosteum with a moth-eaten appearance of the symphysis and rami.

The histologic nature of *calcified medullary defects* has been studied in one case by Ferguson[129] and in two post-mortem examinations by Steel.[130] The particular value of these articles lies in their correlation of roentgenographic and pathological findings. Ferguson regards these defects as degenerated calcified islands of cartilage that did not progress to complete ossification at the time of skeletal growth. Steel, on the other hand, believes that since they commonly occur about the epiphyses they are the result of thromboses of the end arteries.

A classical contribution to present-day knowledge of metabolic bone disease has been made by Albright and Reifenstein.[8] In hyperparathyroidism x-ray examination may demonstrate a wide range of skeletal changes, from severe decalcification with giant-cell tumor formation to relatively normal bone, and renal calculi may offer the only radiographic evidence of this disorder. Burk,[131] in a recent plea for the earlier recognition of hyperparathyroidism, has stressed this point.

Pulmonary osteoarthropathy associated with malignant lesions of the lung parenchyma or mediastinum is well known and quite common. Less frequently noted is its association with congenital heart disease as reported by Means and Brown[132] in the case of a 26-year-old patient with tetralogy of Fallot. The rare condition of idiopathic hypertrophic osteoarthropathy is reviewed by Camp and Scanlan,[133] who analyzed a group of 25 cases, — 21 previously published and 4 additional ones observed by them. This condition occurs predominantly in males at the age of puberty or adolescence and is characterized by the osteoarthropathic syndrome, — clubbing of the digits, enlargement of the bones and joints and thickening of the skin of the face, in the absence of any primary disease. It takes a slowly progressive course to deformity and disability, which are often extreme.

Several chemical agents are capable of producing changes in bone. It is important to recognize that plumbism may be manifest in growing bone even though the lead is inhaled rather than ingested.[134]

Fluorine, if ingested in comparatively sizable amounts over a fairly long period of time, may cause bone peculiarities evidenced by increased density.[135]

Closely allied to bone disease is bone formation that takes place in soft tissue. Soule,[136] during a study of 61 patients who had sustained trauma of the spinal cord with resultant paraplegia of the lower extremities, found that osseous formation in the soft tissues below the level of the spinal lesion indicated a poor prognosis. Associated with these calcifications osteoporosis may be present to a marked degree. Localized absorptive changes have developed at the greater trochanter adjacent to soft-tissue pressure ulcers.[137-139]

Tumoral calcinosis[140] may represent a variant of calcinosis circumscripta. Its etiology is obscure; a familial incidence has been reported.

From a study of identical twins, Vastine and others[141] have shown that the deposition of calcium in costal cartilage is genetically determined.

Lewis[142] has made a preliminary report concerning the radiographic diagnosis of pigmented villonodular synovitis (previously described by Jaffe, Lichtenstein and Sutro[143]), differentiating it from synovial sarcoma. This process is characterized by pigmented yellow-brown outgrowth of synovial villi, affecting the synovia either diffusely or in circumscribed form. Its presence about the knee joint, according to Lewis, should be suspected when the patient is a young adult with signs of monarticular involvement. There is usually no history of injury

and no fever and little discomfort is experienced by the patient. The diagnosis is most likely in cases in which an excessive amount of synovitis of homogeneous density and relatively smooth contour exhibits nodularity of outline in at least some portions. Synovial sarcoma, however, should be suspected if any of the following features are found: nodular soft-tissue masses that are partially or totally outside the joint capsule; the presence of calcium in the soft-tissue masses about the joint; and invasion of bone by the soft-tissue mass. Greenfield and Wallace,[144] in a recent review of the literature and presentation of a case report, show that the results of radiation therapy in villonodular synovitis are good.

Bone Changes Due to Therapy

Vitamin Therapy

Wolbach's experimental work[145] has established a foundation of knowledge concerning the effect of vitamin A in bone development. Vitamin A is essential for activity of epiphyseal cartilage cells; without it they cannot carry out the sequence of growth and maturation or degeneration. Lack of vitamin A causes suppression of endochondral bone growth and cessation of remodeling; appositional growth of periosteal bone continues until inanition supervenes. Excessive administration of vitamin A, on the other hand, accelerates the processes retarded or stopped by lack of the vitamin. In hypervitaminosis-A there is rapid consumption of epiphyseal cartilage, — even premature epiphyseal closure in certain animals and birds. There is marked rapidity of remodeling processes not related to linear growth of bone but definitely related to the rate of activity of epiphyseal cartilage cells. Fractures are very likely to occur at sites where remodeling and normal growth are most active, the lack of firmness of newly formed bone being attributed to failure of the matrix to mature and to lack of calcification in normal appositional bone formation.

Since Josephs,[146] and later Toomey and Morissette,[147] — reported bone changes due to hypervitaminosis-A in infants, a number of articles on this subject have appeared.[148-150] The roentgenographic evidences of the condition are periosteal proliferations, which are common in the ulnas, clavicles, tibias, femurs and metatarsals. The mandible is spared, and the massive lamination seen in infantile cortical hyperostosis is not noted.

Tissue calcification, renal failure and bone or joint abnormalities due to overdosage of vitamin D have been reported with increasing frequency in recent years.[151-155] *That the renal complications associated with this condition may be fatal is not widely recognized.* The clinical findings, observed usually in adults but occasionally in infants, include anorexia, nausea, vomiting, diarrhea, muscular weakness and, at times, bloody polyuria. In most of the reported cases excessive use of this vitamin has been associated with the treatment of rheumatoid arthritis. Calcification may occur in any soft tissue; at x-ray examination it has been observed most frequently in or about joints, bursas and soft tissue adjacent to bone. Associated osteoporosis may be quite severe. On the basis of experimental and clinical observations, it seems that tissue calcification takes place not during the rise of the serum calcium but during periods of relative decline.

Chemical and Hormonal Therapy

The advent of hormonal and chemical therapy has provided a host of new agents that are capable in varying measure of influencing disseminated skeletal lesions due to malignant neoplasms.[156-158] Palliation so gained may endure for months and occasionally for years, although most cases that have been followed for a sufficient length of time have terminated fatally.

After castration for treatment of advanced prostatic cancer, these skeletal lesions have been observed to become denser in three to six months, after which they have shown a tendency to lessen in density and take on the appearance of normal bone.[159] In one case lesions not previously apparent became evident as new zones of density. Utilizing estrogen therapy with and without castration, Herger and Sauer[160] noted favorable response of skeletal lesions in 17 of 48 patients. In 13 cases the bone abnormalities remained unchanged, and only in 4 was actual regression observed; in no instance was there complete disappearance of the bone metastases. Relief from bone pain was much greater than the demonstrable change in the roentgenogram.

Encouraging results of hormonal treatment have been obtained in advanced primary breast cancer, both by the use of steroid hormones and with castration.[161-163] This form of therapy has resulted in regression of bone metastases in 16 to 25 per cent of cases. Although androgens provide a greater relief from bone pain percentage-wise, the demonstrated effect on metastatic lesions is approximately the same. Castration and androgens have been employed largely in premenopausal patients, — estrogens for the postmenopausal group. Histologic studies in a number of cases have shown "varying phases of degeneration by cancer cells, fibrosis, deposition of calcium, and new bone formation."[161] In an occasional instance lytic lesions may gradually become denser and in time approach normal bone. Lesions not previously apparent may become manifest by areas of sclerosis. The roentgenographic changes may not be demonstrable for as long as three months, but bone pain may be lessened in seven to ten days.

Castration has been found effective in the control of metastases from carcinoma of the male

breast in a few cases, favorably influencing both soft-tissue and skeletal lesions.[164]

Radioactive phosphorus has been used in the treatment of metastatic carcinoma of the breast,[165] and regression of bone lesions was noted in 2 of 12 cases. The serious objection to this treatment is that diseased bone takes up P^{32} in only slightly greater amount than does normal bone, and as large doses are necessary, severe depression of the hematopoietic system results.

Radioactive iodine is another isotope that has been employed systemically for the treatment of disseminated cancer. In cases in which functioning, well differentiated thyroid metastases exist this treatment is fairly effective.[166, 167] Thyroidectomy has been performed to enhance the pick-up of I^{131} by the metastatic lesions.[168] Visceral lesions have regressed, and lytic bone changes have either remained stationary or in a few instances have shown evidence of reconstitution.

Nitrogen mustard has been principally utilized in the treatment of Hodgkin's disease and allied lymphomas. Although temporary regression of the soft-tissue involvement has resulted, little or no demonstrable effect on bone changes has been observed.[169]

Aminopterin, a folic-acid antagonist, has afforded palliation in leukemia; in children, regression of destructive bone lesions has followed its use. An interesting radiologic observation has been that with this agent there has been formation at the metaphyses of dense transverse bands such as have been associated with the use of various heavy metals. This formation is thought to represent direct effect of aminopterin on endochondral bone.[170]

Urethane has been employed recently with encouraging results in the treatment of multiple myeloma in 9 out of 16 cases.[171] Relief from pain occurred early, with evidence of bone repair becoming apparent four to six months after the treatment was instituted.

The use of potassium thiocyanate therapy in the treatment of hypertension may lead to the development of osteoporosis, according to Hinchey and his co-workers.[172] Future observation may be of value in elucidating this finding.

Effect on Bone of Radiation Therapy

Spiers[173] is one of the first to point out that supervoltage radiation (600 kv. and over) has an advantage over lower voltages because ionization in bone is much less with hard than with soft radiation. Experimental work on the comparative effects of high-voltage and super-voltage radiation on the epiphyses had been carried out previously.[174, 175] Wilson[176] confirms Spiers' observations; both explain from a physical standpoint what radiologists had already noticed as a practical fact, namely, that less radiation osteitis was attendant on supervoltage than on 200-kv. radiation therapy.

That other forms of irradiation can cause undesirable changes in bone is demonstrated by Wise and others[177] in an experimental study of the effect of diathermy on bone growth. Soft-tissue injury, as well as bone absorption with shortening and resultant deformity, was produced in albino rats in the region of the knee joint. Importance is added to these experimental observations by the report of two infants who, after sustaining diathermy burns, were found to show destruction of epiphyses and subperiosteal new-bone formation.

A recent interesting observation is that frostbite also can produce epiphyseal arrest and delay in growth.[178]

Necrosis of bone following radiation therapy, as noted by Daland,[179] must, although unpleasant, be accepted at times as permissible radiation damage if the treatment of oral cancer is to be adequate. The changes in bone may not become manifest until some time after treatment; furthermore, they may be difficult to distinguish from metastases.

Radiation necrosis of the calvarium has been reported by Camp and Moreton,[180] who emphasize that it may simulate myeloma or metastatic carcinoma. They add that this unfortunate by-product of treatment may be justified, particularly since the calvarium is not subjected to undue stress or strain, when a malignant lesion is to be irradiated.

The development of sarcoma in irradiated bone has been reported so frequently[181-183] that it can no longer be considered mere coincidence.

Pohle and Frank[184] have shown that radiation osteitis may be late in appearing; rib involvement occurred in two cases four-and-a-half and eleven years respectively after radiation treatment for carcinoma of the breast.

Fractures of the neck of the femur following pelvic irradiation have been discussed by Stampfli and Kerr[185] and by McCrorie.[186] Osteoporosis secondary to increased hyperemia and osteoclastic activity are regarded as the chief factors producing pathologic fracture, — damage to the periosteum, blood vessels and bone cells being subordinate causes. The incidence is relatively low and the prognosis with conservative treatment good.

A case of "radiation induced scoliosis" is presented by Arkin and his colleagues.[187] The evidence offered is presumptive rather than factual, but the possibility that x-ray therapy in the spinal area of an infant or young child might result in scoliosis is something to be borne in mind and studied further.

Myelomalacia following irradiation of the spinal cord has also been reported.[188, 189]

Improvements in Diagnostic Methods

No tremendous advances in new technical methods of radiologic diagnosis have been reported, except those dealing with opacification of vessels and the use of radioactive isotopes. Arteriography in the study of blood supply to bone and soft tissue

seems to offer a new approach to suspected malignant lesions and should provide another means of differentiation of osteomyelitis or other infectious processes and neoplasms. Dos Santos,[190] employing arteriograms obtained in rapid succession, has been able not only to demonstrate the anatomic distribution of blood vessels but also to indicate the functional state and activity of the peripheral circulation. His method seems to be applicable in assessing the response of malignant tumors to irradiation and also to distinguishing between benign and malignant tumors. In maligant tumors new blood-vessel formation has been demonstrated, whereas in osteomyelitis no new vessels have been observed, — merely dilatation of those pre-existing. In evaluating the results of treatment in a malignant neoplasm, changes toward obliteration of the blood supply are taken to indicate good response.

Tucker[191] has utilized radioactive isotopes (P^{32}) for detecting aseptic necrosis of the femoral head. Prior to internal fixation of hip fractures P^{32} was injected. At the time of operation, small bone specimens were removed from the greater trochanter and from the femoral head, the samples then being ashed and assessed with a Geiger counter. In two cases in which the uptake of P^{32} in the head was considerably less than in the trochanter, aseptic necrosis developed.

External scanning with a Geiger counter is required to detect peripheral functioning thyroid metastases after administration of radioactive iodine. This method, utilizing other radioactive isotopes, deserves further exploration as a possible aid in distinguishing between benign and malignant primary bone lesions.

The mineral content of bone has been estimated by Henny,[192] who employs a procedure that depends on comparison of the absorption of x-ray in a bone and the absorption in a phantom placed over the same bone. The use of a phantom is not new, but the demonstration of soft-tissue compensation by means of having the phantom radiographed directly over the bone overcomes the shortcomings of older methods, in which the soft-tissue thickness has not been taken into account. Thus far only the femur has been used in these studies, but it may be that demineralization of other bones, the spine and pelvic bones for example, may differ from that of the femur. If, as Henny believes, estimation of the mineral content of the pelvic bones can be made in like manner, the practical clinical value of his investigation will be enhanced.

A similar method for studying the mineral content of the phalanges in rheumatoid arthritis has been tried by Engström and Welin.[193] Determination of the amount of decalcification provides an objective measurement of the severity of the arthritic process.

A number of procedures have been devised to measure accurately the length of an extremity; this is important in the study of not only normal but also abnormal development. It has proved particularly valuable in the study of limb shortening resulting from poliomyelitis.[194, 195] Often it is desirable to have both extremities fully shown. By using a long film (36 to 42 inches) and scanning the entire extremity with a slit-like cone[196] it is possible to show the bones clearly and without distortion. Green and his co-workers[197] employ orthoroentgenography and a long film, successively centering the tube over the hips, knees and ankles, and blocking off the remainder of the film during the respective exposures. (This gives only slight distortion.) Merrill's[198] method allows accurate measurement of the leg length by the use of three exposures on small films, a superimposed scale being included.

In recent years numerous papers have appeared on the subject of arthrography, — the visualization of joint cavities with various contrast materials. This method is a distinct diagnostic refinement and although not new has become more precise with experience gained from studying large series of cases. The knee joint has been most extensively studied by this means where its principal value has been in the detection of tears and other derangements of the menisci.[199-205] Arthrography of the hip has found favor in the investigation of congenital dislocation.[206] With the use of diodrast in the ankle joint, partial diastasis has been demonstrated.[207] The temporomandibular joint has been extensively studied by Nørgaard,[208] who was able, with the use of contrast material, to detect perforation or detachment of the meniscus as well as changes in joint spacing.

The use of flexion and extension roentgenograms of the cervical[209] and lumbar[210, 211] spine has proved of chief value in assessing mobility of vertebral segments and the over-all condition of the intervertebral disks.

Myelography of the lower lumbar spine with the patient in the erect position, using 12 to 15 cc. of Pantopaque, has been found advantageous in reducing the number of false negative and positive diagnoses of disk herniation.[212] Lindblom[213] has been able to demonstrate herniated lumbar disks by the direct injection of water-soluble contrast material into the disk substance through a spinal needle.

As to further progress in the roentgenologic diagnosis of bone disease, the question may be asked: "What do the next ten years hold?" Until new technical methods, such as application of some of the principles of television or image amplification, furnish improvements in demonstrating bone morphology, it seems that the greatest steps ahead will parallel the continued effort at better classification of lesions and, above all, better correlation of roentgenographic and pathological findings.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 37281

PRESENTATION OF CASE

A sixty-year-old woman entered the hospital complaining of periodic episodes of unconsciousness.

The patient was well until about four years prior to admission, when she began to have severe, dull, steady frontal headaches lasting several hours and relieved by common analgesics. These headaches occurred once every two or three weeks and were never accompanied by vomiting. It was noted that during attacks the patient's face would become red and she would assume a glassy stare. About three years before admission she was found lying unconscious in her yard, where she had been hanging out clothes. This episode lasted an hour or two and was followed by extreme fatigue and drowsiness. The patient was not observed to bite her tongue, wet herself or froth at the mouth. She then began to have "falling-out spells," which were preceded by staggering gait, repetitive speech, deviation of the eyes to the right and negativistic behavior, all lasting about thirty minutes. She was usually put to bed by her family when these premonitory signs appeared and would soon become unconscious, with a fiery-red swollen face, noisy breathing and smacking of the lips. These attacks lasted about five hours, speech returning some thirty minutes after consciousness. The patient would have no memory of the episode and would usually ask for food on recovery. These attacks increased in frequency from intervals of several months to once every two weeks. Two years before entry they began to be accompanied by occasional generalized convulsions lasting one or two minutes, at least one of which was noted to begin in the right foot. She began to froth at the mouth during attacks but never bit her tongue. For six months before admission the patient was unconscious at least part of every day and for two weeks she had been in bed unconscious for the greater part of each day. The attacks had no clear relation to meals or time of day. There were no personality changes, motor or sensory changes or episodes of nausea. The headaches continued unchanged throughout the illness.

Five years before admission the patient was found to be hypertensive, with systolic blood-pressure readings as high as 220. For one year she had had frequent attacks of paroxysmal nocturnal dyspnea and habitually slept on three pillows. She had had no operations or other serious illnesses.

Physical examination revealed a well developed, somewhat obese right-handed middle-aged woman lying quietly in bed. She appeared to be extremely apprehensive and was easily moved to tears or laughter. Co-operation was difficult to obtain because of a language barrier. The retinal vessels showed moderate tortuosity and some sheathing near the well outlined disks. The neck veins were flat and the lungs clear. The heart was enlarged to percussion, but heart sounds were of good quality with a normal sinus rhythm. A smooth, nontender liver was felt 2 cm. below the right costal margin.

Neurologic examination revealed no abnormality of speech, station or gait. Except for slight facial flattening on the right the function of all twelve cranial nerves was intact. Deep tendon reflexes were equal and active. There was minimal diminution of tone in the right leg, but motor function was otherwise normal. No sensory abnormalities could be demonstrated. Visual acuity was 18/40 in the right eye, 18/50-1 in the left. The visual fields were intact bilaterally. Psychometric examination showed a borderline normal mental ability with evidence of recent deterioration, probably on an organic basis.

The temperature was 98°F., the pulse 100 and the respirations 16. The blood pressure was 245 systolic, 120 diastolic.

The urinalysis was negative. Examination of the blood disclosed a hemoglobin of 16 gm. and a white-cell count of 8500, with 67 per cent neutrophils. The total protein was 7.54 gm., with an albumin-globulin ratio of 1.7, the nonprotein nitrogen 15 mg., the calcium 9.4 mg., the phosphorus 3.1 mg. and the alkaline phosphatase 4.5 units per 100 cc. Bromsulfalein retention was 9 per cent. A fasting eosinophil count was 28 per cubic mm. A glucose-tolerance test showed a fasting blood sugar of 58 mg., rising to 122 mg. thirty minutes after glucose, to 176 mg. after sixty minutes and to 220 mg. after ninety minutes and falling to 69 mg. per 100 cc. after three hours and forty-five minutes. An electroencephalogram made on the second day was diffusely and nonspecifically abnormal. The spinal-fluid examination was negative. An electrocardiogram was considered abnormal because of nonspecific T-wave changes consistent with left-ventricular hypertrophy or coronary-artery disease. Skull films were unremarkable. The lungs were clear in the x-ray films and the heart was enlarged

in the region of the left ventricle, with a cardiac-thoracic ratio of 15.5:29.8. A gastrointestinal series showed a small hiatus hernia. An electroencephalogram made on the fifteenth day showed more changes than the previous one and was reported as follows: "Voltages bilaterally increased. Slow waves 3-4 per second, bilaterally and synchronously in all leads, especially temporals and frontals on both sides."

The hospital course was marked by repeated seizures, usually occurring in the forenoon and lasting from twenty minutes to two hours. These were characterized by confusion, aphasia, bizarre movements and occasional periods of complete unconsciousness. On at least one occasion the patient became flushed and perspired freely during the attack. On recovery she had no memory for any of these episodes. The fasting blood-sugar determinations during attacks were 51 and 61 mg. per cent. There was no change in heart rate or rhythm, respirations or blood pressure during seizures. No localizing neurologic signs were elicited either during or following attacks. On the thirteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Stanley Cobb*: That this patient was well until four years before admission is probably not entirely correct, because five years before admission the patient was found to be hypertensive, with a systolic pressure of 220, and at that time she also had nocturnal dyspnea and had to sleep with three pillows. I should say that the disease began five years previously and that a year later she began to have the symptom of severe frontal headaches that lasted several hours. The headaches became more severe and lasted longer.

The description of the fits is very important. She had a rather long warning of them; for hours ahead of a fit she might have negativistic behavior, staggering gait and repetitive speech. These began sometimes with the turning of the head and eyes to the right, followed by unconsciousness. Also observed sometimes during these attacks was a smacking of the lips and noisy breathing. Afterwards there was an absolute amnesia for the attack, and on recovering the patient usually asked for food. These attacks increased in frequency and severity up to two years before admission, when they began to be accompanied by a generalized convulsion at times. The remarkable aspect of all this is that over the years of increasing symptoms she did not come to a hospital. Of these convulsions one was observed to begin in the right foot; the other localizing symptom that was only occasionally observed was the turning of the head and eyes to the right, but that was on the same side. There was also salivation but no biting of the tongue. For six months before admission the patient had the attacks every day and was unconscious part of every day. They did not occur especially in the morning and were not related to meals. Then there was added the note that there were no personality changes. I should be skeptical about that, since I think a person who is lying in stupor half the day must have a personality change.

From that story alone, what do I think it was? Because of the headaches and seizures I have to think of brain tumor; because she became red in the face and lay for a long while in stupor I have to consider hyperinsulinism; and because of the high systolic blood pressure I have to consider pheochromocytoma. Moreover, on the list to be ruled out I shall have to put down degenerative diseases of the cerebrum, like Alzheimer's disease. Patients with Alzheimer's disease have cerebral atrophy over the years and often have fits along with it. Since after having these symptoms for five years she was relatively intact on mental examination, I think I can rule out conditions like Alzheimer's disease. A rather more likely condition that I shall add to the list is hypertensive vascular crisis.

On examination she was well developed and obese. She was also right handed, appeared to be apprehensive and was easily moved to tears and laughter. That is of interest. The neurologic examination did not show any abnormality of speech, station or gait. That is important in relation to the other two right-sided symptoms that I have mentioned. The examination of the reflexes showed that they were equal and active. I do not know exactly what "diminution of tone of the right leg" means. I wonder if the right leg was a little weak. At least the right leg was not exactly like the left. There was no suggestion that reflexes on that side were more active than on the other side, which is the thing I would expect if there was a right-sided localization of symptoms. There were no sensory abnormalities except a rather marked diminution in visual acuity, although the eye grounds were practically normal and did not show choked disks. The visual fields were normal also. Then, I think one should ask, was that simply on rough confrontation or were the fields actually examined by the regular parametric examination? I should like very much to know if any abnormality of the visual fields was ruled out or not.

Dr. Edward P. Richardson, Jr.: The central fields were tested with the screen and were intact.

Dr. Cobb: Then there obviously was no lesion of the optic tracts.

There was a blood pressure of 245 systolic, 120 diastolic, and there was a remark that there was no rise in blood pressure when she was having fits. The hypertension was not episodic.

The laboratory data were all within normal limits except perhaps the fasting eosinophil count of 28,

*Chief, Psychiatric Service, Massachusetts General Hospital.

which is somewhat on the low side. The sugar-tolerance test showed 58 mg. fasting, rising to 122 mg. at half an hour and to 220 after an hour and a half, and then fell to 69 mg. at the end of three hours and forty-five minutes. That is extremely significant, but only one test was reported, and I wonder how much I am able to rely on a single examination of sugar tolerance. Did she have more than one sugar-tolerance test, and were the others of a similar nature?

DR. RAYMOND A. ADAMS: That is the only reliable one that she had; others were done.

DR. COBB: I think I should be a lot happier if she had a number of them. The electroencephalogram on the first occasion was diffusely abnormal; it was repeated and showed high-voltage bilateral slow waves of 3 or 4 per second, synchronous in all leads, especially frontal and temporal. That is interesting, but I should like to know if at the moment of the electroencephalogram she was in stupor — or was she alert and responsive?

DR. JOHN ABBOTT: She was awake during the electroencephalogram.

DR. COBB: If she was alert and awake, it was an abnormal record. There was an electrocardiogram that showed an abnormality — some nonspecific T-wave changes.

With the evidence available, am I able to rule out hyperinsulinism? I do not think I am. I only have one sugar curve. I should be better satisfied if she had also had an insulin-tolerance test. If the patient had hyperinsulinism the sugar values ought to have started lower, ought not to have gone up so high and then ought to have returned more rapidly to a low level. The sugar curve looks more like one found in patients with liver disease, but there is nothing else that indicates that she had liver disease except that the liver was a little below the costal margin.

DR. JOSEPH C. AUB: There were two sugar determinations.

DR. COBB: Oh, yes; there were two fasting sugars, 51 and 61 mg. With the evidence at hand — and the evidence is not enough — I shall rule out hyperinsulinism because she does not have the Whipple triad of a sugar below 50 mg., seizures and dramatic relief on intravenous administration of sugar — or at least that is not recorded.

DR. TRACY B. MALLORY: On one occasion when she was very drowsy she was given sugar intravenously; she promptly became alert and co-operative and recognized the physician for the first time.

DR. COBB: That makes me a little shaky in ruling out the hyperinsulinism, but I shall anyway.

If she had a pheochromocytoma there ought to have been a much more marked relation of the fits to rises in systolic blood pressure; the whole story ought to have been much more episodic than it was. With hypertensive vascular crises with seizures she ought to have had more neurologic abnormalities; there ought to have been more extracerebral disease. I think I shall rule that out.

That then leaves me with the condition I think is the most likely — a brain tumor. The remark at the end of the protocol, you observe, is that an operation was performed. I should be very happy to know who operated on her, but I do not know. However, if she had a brain tumor I think affection of the hypothalamus would perhaps be the explanation of the abnormality of metabolism; furthermore, persons who have neoplasms in the region of the hypothalamus have at times shown pictures that are remarkably like the one here described. Penfield* described a patient with tumor of the hypothalamus who had seizures, became red in the face and sweated and had a lot of autonomic symptoms. On the other hand, if this patient had a tumor in the region of the hypothalamus, she should have shown an abnormality in the pituitary region in the x-ray films, and she ought to have had some abnormality of the spinal fluid. Does anyone know if she had a high spinal-fluid pressure?

DR. ADAMS: The pressure was normal.

DR. COBB: And she had had headaches for a long while. A tumor of the hypothalamus ought to produce an internal hydrocephalus and changes in the eye grounds, which she did not have. Then, in localizing the tumor, the smacking of the lips is significant and makes me think of the uncinate gyrus. I can probably rule out temporal-lobe tumor on the normal visual fields. If she had a tumor of the brain it was more likely frontal, and these abnormalities and signs that referred to the region of the hypothalamus or temporal lobe were perhaps due to the change at the base of the brain secondary to pressure — perhaps a herniation. I should not, however, make a diagnosis until I had a pneumoencephalogram. If one suspects a brain tumor and has evidence that is as scattered as this I would want a pneumoencephalogram before actually diagnosing it. Was a pneumoencephalogram made?

DR. ADAMS: No.

DR. COBB: I believe that she had a brain tumor, and the most likely localization is in the left frontal lobe. I believe I have ruled out a pheochromocytoma and probably hyperinsulinism, although there is not enough evidence to rule it out entirely.

DR. DANIEL S. ELLIS: Does islet-cell carcinoma ever metastasize to the brain?

DR. MALLORY: It can produce generalized metastases, but the commonest site of metastasis is the liver. It would be unlikely to metastasize to the brain without evidence of a very large liver.

DR. BERTRAM SELVERSTONE: I should like to ask if the rise in the glucose curve is not slightly abnormal. It was only 122 mg. after thirty minutes and did not rise to a maximum until ninety minutes later.

*Penfield, W. Diencephalic autonomic epilepsy. *Arch. Neurol. & Psychiat.* 22:358-374, 1929.

DR. CHESTER M. JONES: Isn't that partly because we do not know how she had been fed for the last few days, and because she may have had an inadequate amount of fluid for several days before the test was done?

DR. CHARLES S. KUBIK: Dr. Cobb has asked if all the data were included in the summary. Have they been?

DR. ADAMS: No. During one of the attacks a blood sugar of 12 mg. per 100 cc. was obtained, after which 100 cc. of 50 per cent glucose was given intravenously and the patient became normal.

DR. COBB: I thought the blood sugar had not gone below 50; on the data given I had ruled out hyperinsulinism.

CLINICAL DIAGNOSIS

Hyperinsulinism.

DR. COBB'S DIAGNOSIS

Brain tumor, left frontal lobe.

ANATOMICAL DIAGNOSES

Islet-cell adenoma of pancreas.
(*Hyperinsulinism.*)

PATHOLOGICAL DISCUSSION

DR. MALLORY: The clinical diagnosis was hyperinsulinism, and the Surgical Service was asked to perform an exploratory operation to find the pancreatic tumor. The operation was done by Dr. William R. Waddell, and a discrete nodule 1.5 cm. in diameter was found fairly easily on the anterior surface of the pancreas, toward the tail. This was resected. Histologically it was an islet-cell adenoma; no bioassay for insulin was made. Since operation the patient's appetite diminished considerably and she developed mild diabetes. She has not had any further spells in the four months since operation.

DR. AUB: I should like to say that on the data that was presented I do not think anybody ought to make a diagnosis of hyperinsulinism, standing where Dr. Cobb was.

The only thing this recalls to my mind was an extraordinary case of a patient in the Peter Bent Brigham Hospital who was on a starvation diet for twenty-four hours before hypoglycemia was found. I think a diagnosis of hyperinsulinism would not be justified with the lowest blood sugar 50 mg.

DR. KUBIK: I should agree. There were some features that might raise that question, but, as Dr. Cobb stated in the discussion, subsequent tests reported in the clinical account seemed to rule it out.

Would Dr. Cobb like to make any comment about the character of the spells that the patient had in the beginning, when she became drowsy and eventually unconscious without developing a convulsive seizure? Might that be suggestive of hyperinsulinism?

DR. COBB: I think it is suggestive and also might suggest that there was an abnormality in the region of the hypothalamus.

CASE 37282

PRESENTATION OF CASE

A fifty-seven-year-old woman was admitted to the hospital because of cough and fever.

The patient had been well and active until about six weeks before entry, when she developed "flu," characterized by a sensation of a tight band around the chest, occipital headaches, bilateral earaches, aching eyes and slight afternoon chills followed by temperatures of 99 to 100°F. Two to three weeks before admission she began to cough up small amounts of mucoid sputum streaked with blood. An x-ray film of the chest was said to show a blur in the left lung that meant pneumonia, and she was treated with Chloromycetin, penicillin and streptomycin, after which the fever subsided. For one week prior to entry she had had drenching night sweats but no shaking chills. There had been a seven-pound weight loss in the previous three to four months. There had been no chest pain, dyspnea or orthopnea.

The patient had typhoid fever at the age of nineteen and an appendectomy at thirty-six years of age. She had thrombophlebitis of the left leg after childbirth some years ago and had persistent swelling of the left leg in warm weather. There was no history of renal disease or exposure to tuberculosis. The patient had always lived in New England.

Physical examination showed a chronically ill-appearing, thin woman. One observer noted suggestive clubbing of the fingernails and toenails. The eye grounds showed arteriovenous nicking and widening of arterioles with a copper-wire effect. There were no hemorrhages or exudates. The nasal septum was deviated to the right. The heart was normal in size, but the sounds were distant at a rate of 60 to 70 per minute with an irregular rhythm, thought to be either auricular fibrillation or sinus rhythm with frequent premature beats. Examination of the lungs showed dullness, decreased tactile and vocal fremitus, some diminution of breath sounds at the left base posteriorly and dullness at the left apex anteriorly. The liver edge was palpable at the left costal margin on deep inspiration. The legs showed no swelling or tenderness.

The temperature was 99.4°F., the pulse 68 and the respirations 21. The blood pressure was 118 systolic, 80 diastolic.

The urine was cloudy and acid, had a specific gravity of 1.004 and contained no albumin or sugar; the sediment contained 10 red cells and 10 white cells per high-power field. A urine culture showed no growth. Examination of the blood revealed a hemoglobin of 11 gm., a white-cell count of 12,100,

with 77 per cent neutrophils, and a reticulocyte count of 1.5 per cent. A blood Hinton test was negative. The sedimentation rate was 66 mm. per hour. The prothrombin time was 53 per cent of normal. The urine urobilinogen was 0.26 Ehrlich units, the total serum bilirubin 0.2 mg. and the nonprotein nitrogen 44 mg. per 100 cc. A sputum smear and culture were negative for tubercle bacilli and a cytologic examination was negative for tumor cells. An iliac bone-marrow aspiration showed slight erythroid hypoplasia.

An x-ray film of the chest demonstrated within the anterior segment of the left upper lobe an irregular apparently lobulated density, with a somewhat hazy margin, that measured about 8 cm. in its greatest dimension (Fig. 1). There appeared to be slight loss in volume of the left upper lobe, with rather marked narrowing of its bronchus just beyond the bifurcation of the main bronchus. Fluid within the left costophrenic sulcus extended posteriorly within the pleural space to the paramediastinal region. There was some streaky density within the left lower lobe. On the right there was a minute amount of fluid within the costophrenic sulcus. Since the x-ray examination two weeks previously there had been considerable diminution in the size of the left-upper-lobe density, but pleural fluid had formed on the right. A plain film of the abdomen, gastrointestinal series and barium-enema examination were normal; the kidneys were normal in size.

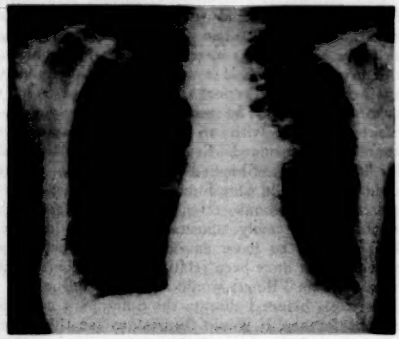

FIGURE 1.

During the seven weeks of hospitalization subsequent chest films showed gradual clearing of the left-upper-lobe lesion, although it never completely disappeared, and there was total clearing of the fluid on both sides. The temperature usually ranged from 98 to 100°F. but occasionally reached an afternoon peak as high as 101 to 102°F. The patient had intermittent nausea. Subsequent voided and catheterized urines gave + to +++ tests for albumin, had a specific gravity ranging from 1.004 to 1.014 and contained ten to "loaded with" red cells, 8 to 10 white cells and occasional to many hyaline and granular casts per high-power field in the sediment. Two weeks after admission the urinary phenolsulfonphthalein excretion was less than 5 per cent in two hours; the nonprotein nitrogen was 56 mg. per 100 cc. The hemoglobin ranged from 7.5 to 11 gm. in spite of 6 transfusions of whole blood, which were given without reaction.

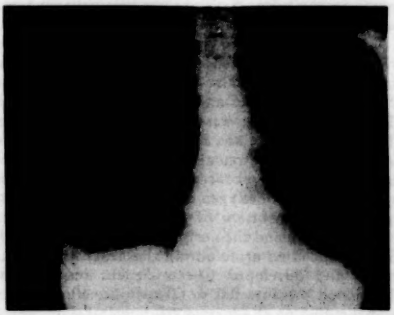

FIGURE 2.

The daily urine output after the first three weeks of hospitalization was usually less than 500 cc., only twice reaching 700 cc., and fluid intake was less than 1000 cc. daily. The weight increased from 130 to 140 pounds, and edema of the back and face developed. The blood pressure remained normal, the highest reading being 142 systolic, 80 diastolic. Four weeks after admission the nonprotein nitrogen was 90 mg., the total protein 6.6 gm., the calcium 8.9 mg. and the phosphorus 4.8 mg. per 100 cc.; the carbon dioxide was 14 milliequiv., the chlorides 95 milliequiv., the sodium 122.6 milliequiv. and the potassium 6.6 milliequiv. per liter. Three days later the nonprotein nitrogen was 120 mg. per 100 cc. and the sodium 116.6 milliequiv. per liter. The patient was given sodium chloride, 1 gm. 4 times daily, and put on a 40-gm. protein diet. No signifi-

cant rise in serum sodium resulted. At about this time she developed a conjunctivitis on the left, which revealed no pathogenic bacteria on culture and cleared rapidly on 30 per cent sodium sulfacetamide and later cortisone eye drops. No signs of thrombophlebitis ever developed. Five weeks after admission a few coarse rales were heard at both lung bases, and three days later a chest film again showed a small amount of free fluid at each base and a wedge-shaped area of increased density posterolaterally in the left lower lobe and mottled densities in the right lower lobe laterally (Fig. 2). Examination of the abdomen revealed ascites. The hemoptyses continued, and crusted blood was noted in the nose. Several tiny hemorrhagic areas were noted far posteriorly on the nasal mucosa.

Four days later, or six weeks after admission, the patient complained of headache, dyspnea and increased nausea. The nonprotein nitrogen was 200 mg. per 100 cc. and the hemoglobin 5.2 gm. The blood pressure was 170 systolic, 90 diastolic. The next day there was a rapid increase in the pulse and respiratory rates, and there were moist rales bilaterally up to the second or third intercostal space. In spite of oxygen therapy, Demerol, tourniquets and transfusion of packed blood cells, the rales increased and the neck veins became distended. She produced no urine during the next twenty-four hours and developed Cheyne-Stokes respirations. The blood pressure fell to 60 systolic, 40 diastolic, and she died on the forty-sixth hospital day.

Differential Diagnosis

Dr. Marian W. Ropes*: I do not know how to group all the complicated features in this case into one picture. The patient had involvement of two major systems, the pulmonary and the renal, and apparently considerable involvement of other systems, probably with cardiac disease, and a liver that was at least palpable. The problems to solve are: What was the nature of these different involvements and were they interrelated?

I shall consider first the pulmonary system. The first attack of symptoms probably represented an acute infection with pulmonary involvement. However, I think there are many features that make it apparent that it was not an uncomplicated acute infection. She had lost weight for three to four months beforehand and the pulmonary disease persisted for about ten weeks before it cleared up. She had suggestive clubbing of the fingers and, although I cannot put too much weight on that, if present it would suggest more serious or more prolonged pulmonary disease. The hemoptysis continued, I judge, throughout the hospital admission. It certainly would be unusual as a complication of an acute infection. Furthermore, the x-ray changes apparently never disappeared. Among the various possibilities of underlying or associated disease one must certainly consider diseases of more chronic nature. Fungus of any type has to be mentioned, but there was no evidence of exposure, there was nothing that would make this typically fungus infection and it would not explain the renal disease.

Tuberculosis, I think, is much harder to discard, and it has to remain as a possibility. There is no question that the pulmonary disease could have been due to tuberculosis, but I think it would have had to be associated with some other infection. The course would be unlikely for tuberculosis even if the pleural fluid and parenchymatous changes were chiefly due to the acute infection; it would be unusual for radiologic changes due to tuberculosis to clear relatively completely and then reappear. However, I think it cannot be ruled out. If it were tuberculosis there would be two possible ways of linking the pulmonary and the renal disease. One would be directly — as renal tuberculosis, which would be unlikely; renal tuberculosis would rarely show as rapid a downhill course and death in uremia in this length of time. If it were miliary tuberculosis, again I would not expect the renal disease to have been so severe. The possibility of amyloid disease associated with an underlying tuberculosis has to be mentioned. Several things are unusual for it, however. She had no albuminuria at the time the red cells were found in the urine, and beginning nitrogenous retention appeared, which would be extremely unusual in amyloid disease. Furthermore, to have amyloid disease secondary to what must have been relatively mild tuberculosis before the final illness would again be unusual.

Perhaps, before I discuss the pulmonary complications further, it would be best to see the x-ray films. I would be particularly interested in knowing whether the narrowing in the bronchus and the small size of the upper lobe were still present when the other condition cleared up.

Dr. Joseph Hanelin: The films we have cover a span of about five and a half weeks. The first set of films, the posteroanterior and lateral projections, show the density that was described in the left upper lobe (Fig. 1). I would certainly have thought of carcinoma as the first possibility, except that in outside films made two weeks before admission the density had been considerably larger. There is a left pleural effusion that extends into the paramediastinal region. A minute amount of fluid is present at the right base. The pleural-fluid collections have cleared eleven days later and the left-upper-lobe lesion is further reduced in size. About three weeks later this wedge-shaped density has developed in the left lower lobe, and there are streaks of density at the right base and a minute amount of fluid at either base (Fig. 2). The lesion at the left hilus has contracted further. The pulmonary lesions were regarded as areas of pneumonia or possibly of infarction.

*Associate physician, Massachusetts General Hospital.

DR. ROPES: Can you see whether the bronchus remains narrowed?

DR. HANELIN: It seemed narrow on the first set of films. I do not think we made that observation afterwards. The films of the stomach and colon add nothing, and the kidneys appear grossly normal in size and contour.

DR. ROPES: That just adds to the varied impressions I had clinically and does not verify any of them. The next type of pulmonary involvement to discuss is neoplasia. If it was a malignant process, there was much to suggest that it was primary. One of the reasons that I was interested in the persistence of the narrowing of the bronchus and small size of the lobe was to determine the presence of obstruction that would be most likely on the basis of a malignant process — or possibly tuberculosis. If this were a primary pulmonary cancer, the renal disease would have to be explained on another basis. However, primary cancer still cannot be ruled out. One would have to explain the improvement on the basis of an acute superimposed infection that was then subsiding. In thinking of metastatic malignant processes that might explain the picture, I would have to mention hypernephroma; however, nothing in the pulmonary findings was characteristic of hypernephroma. I think that it cannot be ruled out but would be very unlikely. Again, the rapidly downhill renal course would be somewhat unusual. I would expect a period of at least a few weeks between the early mild uremia and death.

When it comes to the question of infarction, there were a number of points in favor of infarction. The final x-ray films would surely add weight to a diagnosis of infarction. It seems quite likely that the patient did have, in addition to whatever else she had, pulmonary infarction terminally. Whether or not she had it at the beginning I find more difficult to decide, but I rather doubt it. One could, of course, attempt to explain the renal disease on the basis of infarction. Sources of emboli were not too apparent. I think the old thrombophlebitis need not be considered too seriously. The cardiac situation is hard to explain. If she had auricular fibrillation, it is conceivable that she had pulmonary and renal infarction produced by emboli from the heart. There was no further evidence about the heart disease than the statement that there was possible fibrillation on admission. If fibrillation was present, I should think it was on the basis of arteriosclerotic heart disease. Fibrillation could have been a possible source of emboli, although it seems unlikely.

To discuss the renal disease, there was evidence that it was present at the time of admission, but at that time there was no albumin, only a few cells and slight nonprotein-nitrogen retention. She had a moderate uremia, which progressed rather rapidly. I have already mentioned amyloidosis as a possible cause of the renal disease, but the course would be unusual and there was no evidence of a source. I doubt that it was so called primary amyloid disease. Tuberculosis cannot be ruled out either in the chest or in the kidney, but I think the rapid course was somewhat against it. I have mentioned hypernephroma and renal infarction, both of which I would tend to rule out.

Glomerulonephritis has to be considered very strongly. She had a hemorrhagic renal disease coming on in the course of or after an infection. There was very little in the course that would be entirely against glomerulonephritis. The absence of hypertension would be unusual. The blood pressure finally reached 170 systolic, 90 diastolic, but for weeks there was no hypertension. However, glomerulonephritis could not be ruled out on this basis. Arteriosclerotic or vascular nephritis is another type that has to be considered. She had evidence of arteriosclerotic changes in the eye grounds and perhaps in the heart beyond those one would expect at fifty-seven years — so much so that one would have to think of a generalized vascular disease of the type of periarteritis nodosa. Again, although this might explain the renal disease I would think it very unlikely as an explanation of the pulmonary findings.

I am sure one has to mention the medicines that were given to the patient in terms of the possible relation to renal disease. I rather doubt that any of the many drugs she received caused the renal disease, but I think the possibility cannot be ruled out. We still know too little about the rare cases of renal disease produced by the antibiotics. I think she received too little sulfacetamide to think of it as a possible complication, and it was given after she had evidence of renal disease.

In lining up the various conditions that could cause the pulmonary and the renal involvement, I find it difficult to choose among the various conditions. I have to guess which combination best explains the entire disease, and I think from the collection I shall choose glomerulonephritis, with acute pulmonary infection, and pulmonary infarction at the end, but I suspect that she also had a primary malignant process in the lung. That presents a good many conditions to explain the picture, but I find myself unable to relate the renal and pulmonary complications otherwise.

DR. EDWARD B. BENEDICT: I would rather put the primary tumor in the kidneys — renal-cell carcinoma with metastases to the chest and possibly to the brain to explain the final headaches.

DR. ROPES: Dr. Colby asked me why I did not think she had renal thrombosis. I believe death would have come much sooner if that had been the case.

DR. FLETCHER COLBY: I do not think that is necessarily true. That would have been a good way

to link up the pulmonary disease with the renal disease.

Clinical Diagnoses

Uremia.
?Acute glomerulonephritis.

Dr. Ropes's Diagnoses

Acute pulmonary infection.
Glomerulonephritis.
Pulmonary infarction (terminal).
?Primary cancer of the lung.

Anatomical Diagnoses

Polyarteritis nodosa, generalized with marked renal involvement.
Hemorrhagic pneumonitis, uremic.
Cholesterol pneumonitis.

Pathological Discussion

Dr. Tracy B. Mallory: I do not believe it is possible to link together the original pulmonary lesion and the renal disease. They appear to be entirely unrelated lesions. The left upper lobe of the lung was somewhat smaller than normal at autopsy, appeared a little firmer and was very pale, with a yellowish color — an appearance that we have come to associate with a lesion we have called cholesterol pneumonitis[1, 2] and that has also been called endogenous lipoid pneumonia. I believe, Dr. Hanelin, that the early x-ray findings would be compatible with such a diagnosis, as it has frequently been confused with bronchogenic carcinoma.

Dr. Hanelin: Yes.

Dr. Mallory: It seems probable that in some of these cases one should be able to see either foam cells or cholesterol crystals in the sputum. Without that I do not see how an ante-mortem diagnosis could be made without an exploratory operation.

The renal lesion was a somewhat complicated one. The kidneys grossly were slightly enlarged and showed many pin-point hemorrhagic foci suggesting the gross appearance of an acute glomerulonephritis, and glomerulonephritis was found histologically — a little unusual, however, in appearance, in that many of the glomeruli showed a considerable degree of fibrinoid necrosis. It has recently been pointed out by Davson[3] that this type of glomerular change is often seen in patients who suffer from polyarteritis nodosa. In this patient multiple arterial lesions of that type were found, most numerous in the kidney; a few were scattered elsewhere in the heart, lungs, thyroid, periadrenal fat and pancreas.

A second type of lesion was present in the lung that I believe was terminal and not related to the cholesterol pneumonitis or the polyarteritis nodosa. It was largely limited to the lower lobes, which were very heavy, relatively solid, deeply hemorrhagic — a type of change that is frequently seen in patients dying in uremia and is also very similar to the so-called rheumatic pneumonia seen in patients dying in the acute stages of rheumatic infection. There has been a long-standing argument between the departments of Radiology and Pathology in this hospital about whether it constitutes a form of pulmonary edema or a form of pneumonia or pneumonitis. The radiologists generally wish to call this edema. It is sufficiently characteristic in its x-ray appearances that on one occasion Dr. Schatzki looked at the chest film and made a presumptive diagnosis of nephritis. When that was reported back to the ward, the physicians for the first time found red cells in the urine and an elevated nonprotein nitrogen. I cannot tie this up in any way with the older pulmonary lesion that was in the left upper lobe — the one that we have called cholesterol pneumonitis.

A Physician: Was the wedge-shaped lesion in the lung an infarct or this later type of lesion?

Dr. Mallory: That was the lesion I have just been describing — the uremic pneumonitis. We did not find any characteristic areas of pulmonary infarction.

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ACTH AND CORTISONE IN INFECTION

THE striking effects of adrenocorticotrophic hormone (ACTH) and cortisone in suppressing the manifestations of inflammation in many conditions have led to the widespread use of these agents in many diseases in which no benefits have been demonstrated, and often without regard to their possible deleterious effects. Entirely apart from the toxicity of these agents, which may be ascribable directly or indirectly to their metabolic effects or to their endocrine functions, there is increasing evidence that these agents, particularly cortisone, may actually increase the severity of, or enhance the susceptibility to, many infections in experimental animals and in man. Much of this evidence is included in a recent review in this journal,[1] but a few of the reports dealing directly with the effect of ACTH or cortisone therapy on infections may be summarized here briefly.

Kass, Ingbar and Finland[2] reported the effects of ACTH, given alone, without antimicrobial agents, to 5 patients with pneumonia — 3 with pneumococcal and 2 with viral pneumonia. In all these patients clinical improvement, with defervescence and relief of symptoms and signs of acute toxemia, occurred promptly after ACTH administration was begun. In the 3 cases of pneumococcal pneumonia, however, there was no effect on the organism; in one of these patients bacteremia persisted for thirty-six hours; in another, rusty sputum persisted for several days after the temperature was normal and the patient felt clinically well. In addition, one patient had an extension of his pulmonary lesion and subsequently developed empyema, and one of the patients with primary atypical pneumonia had a severe and protracted course. Smadel and Woodward and their respective associates[3, 4] also were able to show a dramatic clinical effect in patients with typhoid fever after administration of cortisone, either alone or as a supplement to chloramphenicol therapy. In their patients also the organisms were not affected, and relapse and complications in individual cases were not prevented.

Deleterious effects, however, have been demonstrated more clearly in experimental animals. Thomas and his co-workers[5] showed that when cortisone was administered for two or three days before and after an infection had been produced in the skin of rabbits with Group A hemolytic streptococci, there was little or no local reaction but the rabbits regularly developed extensive bacteremia and died in four to twelve days. In these cortisone-treated animals, colony-like deposits of streptococci were observed in the interstitial tissues of the heart and kidneys in many instances. Animals similarly infected but not treated with cortisone showed only a mild local reaction and occasional transient bacteremia, but all survived. These workers also showed that when cortisone was given together with intravenous injections of some bacterial toxins to rabbits there was a marked cortical

necrosis of the kidneys. Animals given cortisone alone or the intravenous toxin alone failed to show such renal lesions.

Glaser and his co-workers[8] produced streptococcal and pneumococcal pneumonia in rats by intrabronchial inoculation. The survival rates from such infections in all their experiments were less favorable among animals treated with cortisone. The lesions in cortisone-treated animals contained excessive amounts of acellular edema fluid, in which there were many more bacteria than had ever been seen in analogous lesions from control animals that did not receive cortisone. Cortisone alone was shown to exert no growth-stimulating effect on the bacteria, nor did it influence significantly the phagocytic activities of the leukocytes that eventually appeared in the lesion.

Abernathy[7] infected mice, guinea pigs and rabbits with various types of brucella organisms and treated some of these animals with cortisone. The cortisone-treated animals had a higher death rate and their lesions were more widely distributed than in comparable controls not treated with cortisone. The hepatic granuloma was converted into a necrotic lesion by cortisone therapy.

Kligman and others[9] studied the effect of cortisone on the pathologic response of guinea pigs infected subcutaneously with a trichophyton, vaccinia virus and *Staphylococcus aureus*. The course of the lesions was adversely influenced by the cortisone in each instance. Furthermore, the sensitivity to trichophyton or to killed vaccinia virus in animals rendered allergic by infection was not diminished by cortisone.

There is even more evidence that experimental infection with *Mycobacterium tuberculosis* is aggravated by cortisone. D'Arcy Hart and Rees[9] showed that cortisone markedly aggravated both the acute and the chronic type of tuberculosis in mice. In the hormone-treated animals the mortality was increased; the lesions became more necrotic and showed much larger numbers of bacilli. This was interpreted as a marked breakdown in the resistance of the animal, due to the cortisone treatment. Several treated animals died with necrotic foci in the liver, possibly because of increased susceptibility to organisms other than the tubercle bacillus.

Spain and Molomut[10] also produced experimental infections in guinea pigs with a human virulent strain of tubercle bacilli. These animals were divided into 4 groups: one was treated with saline solution, a second with cortisone, a third with streptomycin and a fourth with cortisone and streptomycin. In all the animals treated with cortisone the lesions appeared to be more extensive, more widely distributed and less well localized. Even the beneficial effect of streptomycin was partly lost by the additional use of cortisone.

The albino rat normally responds to infection with human virulent tubercle bacilli with a chronic granulomatous nonfatal process in which caseation is relatively inconspicuous. Michael, Cummings and Bloom[11] showed that this infection could be markedly altered by cortisone. The majority of the rats that were infected with such organisms and treated with cortisone died of tuberculosis, and at histologic examination their tissues showed diffuse lesions that contained fewer inflammatory cells but numerous acid-fast bacilli. Other workers[12] have shown that cortisone also overcomes the beneficial effects of vaccination in mice that are subsequently infected with human virulent *Mycobacterium tuberculosis*. In such studies the lethality of similar virulent organisms in nonvaccinated mice did not seem to be altered, but the susceptibility of mice to strains of low virulence was significantly enhanced.

Experimental syphilomatous lesions induced in rabbits by intradermal or intratesticular inoculation of *Treponema pallidum* was shown by Turner and Hollander[13] to be markedly altered by cortisone. The lesions became spongy and contained excessive amounts of mucoid material and unusually large numbers of treponemes. When the cortisone treatment was stopped there was a rebound phenomenon in which the lesions reached an unusual size.

Shwartzman[14] has shown that ACTH and cortisone in combination or cortisone alone may produce a marked acceleration of poliomyelitis infection in mice. Cortisone also produced an extraordinary enhancement of susceptibility to poliomyelitis infection in hamsters; in these animals it gave rise to a violent and uniformly fatal disease.

ACTH alone failed to produce these effects. In human poliomyelitis a carefully controlled study showed no benefit from ACTH.[15]

Attention has also been called to the possible harmful effect of treatment with cortisone or ACTH in patients who have active or latent peptic ulcers. Beck and his colleagues[16] at the Royal Victoria Hospital in Montreal reported 2 cases of acute peritonitis occurring as a complication during ACTH administration, — for Hodgkin's disease in one instance and for periarteritis nodosa in the other. It is of interest that these patients had no fever, a normal pulse rate, no leukocytosis and, in one case, no abdominal rigidity. Pain and absent peristalsis, and in one case diminished liver dullness, were the only features of the underlying condition. It is, therefore, important to appreciate that certain signs and symptoms of acute abdominal emergency may be obscured during ACTH administration. Smyth[17] reported 3 cases in which ACTH apparently had a markedly deleterious effect on peptic ulcer. In one of his cases the treatment may actually have led to the patient's death. Similar unfavorable results in ulcer patients have been encountered by others.

Other instances of infections, sometimes with bacteremia, arising during the course of treatment of patients with ACTH and cortisone for other conditions have been encountered in many clinics. In many cases the evidence of the infection was obscured by the lack of fever, the sense of well-being and the increased appetite that such patients may sometimes have during ACTH or cortisone therapy in spite of the progression of infection and even in the presence of bacteremia. It therefore seems prudent to avoid the use of these agents in patients known to have chronic or latent infections or peptic ulcers or similar conditions that might be aggravated by such treatment.

Although the apparent sense of well-being temporarily engendered by the use of ACTH or cortisone may prompt some physicians to use these agents in certain severely ill and toxic patients during the course of infections, it seems highly important that they be used with the greatest caution and for the briefest possible time, or preferably not at all, under such conditions. Under no circumstances should these agents be considered as substitutes for specific antimicrobial therapy. Indeed, the experience with tuberculosis in animals suggests that, if anything, the use of these agents in combination with antibiotics may actually reduce the benefits derived from the specific antiinfectious agent.

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JOHN CLARENCE CUTTER

One hundred years and two days prior to the date of this issue of the *Journal* Dr. John Clarence Cutter was born in the town of Warren, Massachusetts. He was the son of Calvin Cutter, author of "Cutter's Physiology" and surgeon to Burnside's Second Brigade, and Eunice Powers, "a woman of the old school of culture"; a brief account of his life by Sarah H. Powers appeared in the *Boston Medical and Surgical Journal* on November 9, 1916.

Cutter was graduated from the Agricultural College at Amherst in 1872, devoted a year to the pursuit of literature in Lippincott's publishing house,

spent two years in Dartmouth Medical School and then transferred to Harvard Medical School, from which he graduated in 1877. In the following year he went to Japan as professor of physiology and comparative anatomy at the College of Agriculture in Sapparo, on the Island of Yezo; shortly after his arrival he was appointed consulting physician to the Imperial Colonial Department.

He returned home in 1887 and sailed in the following year for Europe, where he studied dermatology in Berlin and Vienna. In 1890 he opened an office for the practice of medicine in Worcester, Massachusetts, but was forced to retire in 1893, invalided by an infection acquired during the course of a surgical operation at which he had assisted. During his brief, active career of only fifteen years he had paid off his father's debts of several thousand dollars, with interest, and revised his father's books. In 1897 he sustained his first shock, which left him partially paralyzed; the second and fatal shock occurred on February 2, 1909.

Dr. Cutter's will revealed that the residue of his estate, after certain small bequests were paid, including one of $500 for the erection of a drinking fountain on the grounds of Sapparo College, should go to Harvard Medical School, which was

> to devote one-half the net income to the maintenance of an annual course of lectures upon preventive medicine. Any money not annually so expended shall be added to the principal. Lectures shall be styled "The Cutter Lectures on Preventive Medicine." They shall be delivered in Boston, and shall be free to the medical profession and to the press.

The first lecture was delivered on March 13, 1912, by Dr. William H. Park, the late revered director of the research laboratories of the Department of Health, New York City, on "Observations on Dosage and Methods of Injecting Antitoxin in the Treatment and Prevention of Diphtheria and Tetanus." The sixty-sixth and most recent lecturer was Dr. Hugh M. Sinclair, fellow of Magdalen College, Oxford, and director of the Laboratory of Human Nutrition of the university, whose address on "Nutrition Surveys of Population Groups" appears elsewhere in this issue of the *Journal*.

This early belief in the part that preventive medicine might play in influencing the destiny of man has been faithfully maintained by the Harvard Medical School and the Harvard School of Public Health. The list of Cutter lecturers, from both this country and abroad, has included many eminent authorities who have given their best on a variety of subjects.

Thus are the channels of science, of culture and of beneficence opened and maintained in a stable society. It can rightly be said, a hundred years after the birth of John Clarence Cutter: "By their fruits ye shall know them."

ACADEMY OF MEDICINE

THE Massachusetts Medical Society, as World War II drew to its close, began to take a special interest in furthering the educational opportunities that might be offered to returning medical officers. The program that was then organized by the Society's Committee on Postgraduate Medical Education to help to reorient physicians in civilian medicine has established a conspicuously successful pattern of the way in which a state medical society can operate along academic lines.

The clinics and other exercises that have been presented all over the State by the many circuit-riding members of the "faculty" have been augmented by a course of lectures given annually in Cambridge or Boston; the sixth of these courses took place this spring. In addition, a three-day teaching conference was held at the University of Massachusetts in Amherst last September. Mention should also be made of the equally successful though somewhat less ambitious postgraduate assemblies that have been planned for the Council of New England State Medical Societies by another committee of the Massachusetts Medical Society and held each fall for the past nine years.

With such a record of successful achievement behind it, it is natural that the Committee on Postgraduate Medical Education should take a still longer view of its opportunities and plan a more permanent as well as a more effective organization for postgraduate instruction. This has already begun, as is indicated in Dr. Ellis's letter published on another page of the *Journal*.

As Dr. Ellis announces to the physicians of Massachusetts, a survey of postgraduate medical

education in the State has been inaugurated under the sponsorship of his committee. It is expected that this survey, which is being implemented through contributions from each of the three medical schools in Boston, the Lahey Clinic, the Massachusetts Heart Association and the American Foundation for Infantile Paralysis, will study the educational facilities available, co-ordinate them and act as a central clearing-house for information.

Eventually, it may be hoped, the organization under which the survey is being conducted will develop into a more permanent institution: one that will be able to enlarge and improve these already impressive educational opportunities for physicians, whose education, as they themselves well know, is never completed.

University of Pennsylvania. Medical Department. Eighty-sixth Session, 1851-52. . . . Amount of Fees for Lectures in the University, $105. Matriculating fee (paid once only), $5. Hospital fee, $10. Practical Anatomy, $10. Graduating fee, $30.

Boston M. & S. J., *July 16, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DUDLEY — Charles Dudley, M.D., of Kingston, died on June 28. He was in his eighty-third year.

Dr. Dudley received his degree from Harvard Medical School in 1897. His widow, a daughter and a sister survive.

FALLON — John Fallon, M.D., of Shrewsbury, died on June 21. He was in his fifty-first year.

Dr. Fallon received his degree from Harvard Medical School in 1923. He was a councilor of the Massachusetts Medical Society, a trustee of the Boston Medical Library, a member of the New England Obstetrical and Gynecological Society and the New England Cancer Society, and a fellow of the International Society of Surgery.

His widow and six children survive.

GARDINER — Harry M. Gardiner, M.D., of Medfield, died on April 3. He was in his forty-seventh year.

Dr. Gardiner received his degree from Hahnemann Medical College in 1931. He was assistant superintendent of the Medfield State Hospital. He was a member of the American Board of Psychiatry and Neurology, the American Psychiatric Association and the New England Society of Psychiatry and a fellow of the American Medical Association.

LEAVITT — Mary A. Leavitt, M.D., of Boston, died on May 2. She was in her seventy-fifth year.

Dr. Leavitt received her degree from Boston University School of Medicine in 1902.

A brother and a sister survive.

THOMAS — John D. Thomas, M.D., of Boston, died on December 4. He was in his fifty-ninth year.

Dr. Thomas received his degree from the College of Physicians and Surgeons, Boston, in 1929. He also graduated from Université de Lausanne Faculté de Médecine, Switzerland, in 1934.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SOUTH DAKOTA ACCEPTS MASSACHUSETTS REPORT

This department has just been informed that the South Dakota Department of Public Health will accept premarital-examination certificates completed by Massachusetts physicians. It is suggested that South Dakota be added to the list of those states accepting Massachusetts reports that was published in this column on February 1, 1951, pages 194 to 196.

CORRESPONDENCE

SURVEY OF POSTGRADUATE MEDICAL EDUCATION

To the Editor: Physicians of Massachusetts will be interested in the survey of postgraduate medical education that is being made under the sponsorship of the Committee on Postgraduate Medical Education of the Massachusetts Medical Society. It is now accepted by all that doctors in practice need the opportunity of continual re-education in medicine, particularly as regards new developments in the field. Although Boston and the Commonwealth as a whole, through the medical schools, the hospitals, special societies, the Department of Public Health and the program of the Massachusetts Medical Society itself, provide such opportunities, there has hitherto been no co-ordination of the facilities and no clearinghouse where all pertinent information can be found. The present survey has been set up to remedy this situation. Through it, it is expected that a central clearinghouse of all available information pertaining to postgraduate medical education in this state will become an actuality and also that positive steps will be taken to widen and improve the opportunities for such education. The potentialities of what may well develop from this study are very great indeed.

The survey has been made possible through contributions already received from each of the three medical schools in Boston, from the Lahey Clinic, the Massachusetts Heart Association and the American Foundation for Infantile Paralysis. It is anticipated that before this letter has been published additional contributions from several other agencies will have been made. The Massachusetts Medical Society has already provided office space in its new headquarters at 22 Fenway and will be asked to make an appropriation for the support of this work. An executive secretary for this survey, Mrs. Charlotte Troutwine, has been engaged and is at work.

It is to be hoped that all individuals and all institutions and agencies in any way concerned with the postgraduate education of doctors will co-operate fully in this study, not only in supplying information as requested but in offering suggestions and constructive criticism. They should not wait until approached but should take the initiative by contact-

ing Mrs. Troutwine, at the office of the Massachusetts Medical Society.

Very truly yours,

LAURENCE B. ELLIS, M.D.
Chairman, Committee on Postgraduate Medical Education
Massachusetts Medical Society

BOOK REVIEW

In Defense of Mothers or How to Bring Up Children in Spite of the More Zealous Psychologists. By Leo Kanner, M.D. Second printing. 8°, cloth, 167 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1950. $3.00.

Dr. Kanner is a pediatrician who has specialized in the psychotherapy of parents. This little book, first published in 1941, contains some of the desensitization, reassurance and directive therapy he has been offering to certain types of mildly anxious mothers. It is addressed primarily to women whose approach to motherhood reflects some of the current obsessive-compulsive trends in our culture, and the author declares his specific aim to be the safeguarding of parents from the alarums and excursions of overzealous dilettantes in the field of child psychology. Thus he has adopted a playful, anti-intellectual, "common-sense" tone in pleading for relaxed moderation in child rearing. Some of the topics discussed in this way include maternal overprotection, hypochondriasis, feeding problems, thumbsucking, sex enlightenment and character training.

The author recommends love and respect for the child as a person, together with a realistic acceptance of his immaturity and limitations. Perhaps Dr. Kanner believes that if these recommendations are actually carried out there will be no need to discuss such topics as toilet training, temper tantrums, sibling rivalry, enuresis or nail-biting. At least, these topics are omitted from the present treatise. And, although he does refer to masturbation in his discussion of thumbsucking, he makes no attempt to deal with the parental tensions usually aroused by this subject.

This book is written in a forthright style that is both anecdotal and amusing. It is perfectly harmless and even easier to read than Spock's best-seller. One may prescribe it with confidence for any mother who has had at least an eighth-grade education; its reading is especially indicated for those women who tend to be somewhat anxious, overconscientious or pseudo-sophisticated.

CHARLES P. FONDA, PH.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Disorders of the Blood: Diagnosis: pathology: treatment: technique. By Sir Lionel E. H. Whitby, C.V.O., M.C., M.A., M.D. (Cantab.), F.R.C.P. (Lond.), D.P.H., Regius Professor of Physic, University of Cambridge; and C. J. C. Britton, M.D. (New Zealand), D.P.H., physician and haematologist, Prince of Wales's Hospital, London, consulting haematologist, Queen Mary's Hospital, Roehampton, and pathologist, St. Andrew's Hospital, Dollis Hill, the Finchley Memorial Hospital and the Hendon District Hospital. Sixth edition. 8°, cloth, 759 pp., with 12 colored plates and 94 illustrations. Philadelphia: Blakiston Company, 1950. $8.00.

This British book was first published in 1935, and the fifth edition (1946) was translated into Spanish. The chapters on coagulation, the hemolytic anemias, leukemia, hemoagglutination, pigment metabolism and technic have been extensively revised. Eighty-five pages, as well as illustrations, have been added to the text. The authors have surveyed the literature through 1949. Extensive bibliographies are appended to the various chapters. The printing was done in Great Britain, and the publishing is excellent. The textbook should be in all medical libraries and in the collections of all specialists on blood.

Essay on the Cerebral Cortex. By Gerhardt von Bonin, M.D., professor of anatomy, University of Illinois College of Medicine. 8°, cloth, 150 pp., with 32 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $3.75.

These essays begin with an interesting historical survey from the time of Franz J. Gall (1758–1828) to the present. This is followed by a theoretical and phylogenetic introduction on the relations between neurons, and on the brain of vertebrates. The succeeding essays discuss the general morphology of the cortex, sensation, action, prediction and emotion. An extensive bibliography of 213 references concludes the text. The literature is evaluated throughout the text. Unfortunately, there is no index, although one would have been invaluable in this type of survey monograph.

Freud: Dictionary of psychoanalysis. Edited by Nandor Fodor, associate of the Association for the Advancement of Psychotherapy, and Frank Gaynor. With a preface by Theodor Reik. 8°, cloth, 208 pp. New York: Philosophical Library, 1950. $3.75.

This dictionary is a complete glossary of all the basic terms in psychoanalysis as explained and defined by Dr. Freud. The terms are arranged in alphabetical order.

The Legacy of Maimonides. By Ben Zion Bokser. 8°, cloth, 128 pp., with frontispiece. New York: Philosophical Library, 1950. $3.75.

The author, in this philosophical essay, attempts to portray the inner system of ideas contained in the varied writings of Moses Maimonides. It is based primarily on the discussions in the *Guide to the Perplexed.*

The Biochemistry of B Vitamins. By Roger J. Williams, Robert E. Eakin, Ernest Beerstecher, Jr., and William Shive, University of Texas, Austin, Texas. 8°, cloth, 741 pp., with 50 tables. New York: Reinhold Publishing Corporation, 1950. $10.00. (American Chemical Society Monograph No. 110.)

This comprehensive work is one of the Chemical Monographs of the American Chemical Society. The text is divided into four sections: characterization, distribution, assay and biogenesis; catalytic functions; the role of the components of the vitamin B complex in animal and plant organisms; and the comparative biologic activities of vitamin B and related compounds. Extensive bibliographies are appended to the various chapters throughout the text. The material is well arranged, and there is a good index. The publishing is excellent, and the book constitutes an essential reference work. It should be in all medical and chemical libraries and accessible to biochemists and physiologists.

Facial Paralysis, Being a Treatise on a Clinical Classification of Paralysis of the Facial Nerve. By J. Parkes Findlay, M.B., Ch.M. 8°, cloth, 45 pp., with illustrations. Published by the author and distributed by Angus and Robertson, Limited, Sydney, Australia, 1950. 17/6.

In this special monograph the author presents the results of his investigations on facial paralysis observed in cases since 1933. He discusses the anatomy and variations of the facial nerve and its examination and the symptomatology, diagnosis, treatment and prognosis of facial paralysis according to his classification of four types.

Microbiology With Applications to Nursing. By Catherine J. Witton, M. A., associate professor of biology, Simmons College, Boston. 8°, cloth, 692 pp., with illustrations. New York: McGraw-Hill Book Company, Incorporated, 1950. $4.50.

This textbook for nurses could be used to advantage by physicians to gain a basic knowledge of the science of microbiology. The whole field of the subject is covered in seven

parts and three appendixes. The early parts deal with the basic structure and activities and control of micro-organisms, the sources and modes of infection, and infection and immunity. The following chapters discuss the pathogens or bacteria, pathogenic organisms other than bacteria, including the rickettsia, viruses, actinomycetes and fungi, protozoa and worms. The appendixes are devoted to laboratory methods, literature and teaching aids, and the classification of medically important schizomycetes. The material is well arranged and written. There is a comprehensive index, and the publishing is excellent.

Sir William Osler: Aphorisms from bedside teachings and writings. Collected by Robert B. Bean, M.D. Edited by William B. Bean, M.D. 16°, cloth, 159 pp. New York: Henry Schuman, Incorporated, 1950. $2.50.

This collection of sayings of Dr. Osler is divided into five sections: the medical student; the ethos; the patient; the great republic of medicine; and epitomes. Dr. Bean jotted down many of the aphorisms, and collected many others from the published writings of Dr. Osler. There are 357 items, and a bibliography of sources is appended to the text.

Acute Head Injury. By Joseph P. Evans, M.D., Ph.D., associate professor of surgery and director, Division of Neurological Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio. 8°, cloth, 115 pp., with 24 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.25. (Publication No. 60, American Lecture Series.)

Dr. Evans discusses the various aspects of head injuries, including injuries to the scalp, fractures of the skull, meningeal hemorrhage and cerebral trauma. A bibliography of eighty pertinent references is appended to the text. This monograph furnishes the latest information on the subject and should be in all medical libraries and available to all surgeons.

On the Experimental Morphology of the Adrenal Cortex. By Hans Selye, M.D., Ph.D., D.Sc., F.R.S.(C), professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal; and Helen Stone, B.Sc., Institute of Experimental Medicine and Surgery, University of Montreal. 8°, cloth, 105 pp., with 12 plates. Springfield, Illinois: Charles C Thomas, 1950. $2.25. (Publication No. 74, American Lecture Series.)

Dr. Selye, a recognized authority on endocrinology, in this monograph presents the results of his experiments concerning the effect of various hormone preparations on the adrenal cortex.

The Prostate Gland. By Herbert R. Kenyon, M.D., associate clinical professor, Department of Urology, New York University–Bellevue Medical Center. 8°, cloth, 194 pp. New York: Random House, 1950. $2.95.

Dr. Kenyon has written a sound book for the layman on the prostate gland, its function and its disorders. The small book is well published and should be in all medical collections for the laity. The popular medical books of today, written by authorities in their particular fields, are far removed from those of yesterday, which were more or less irregularly presented or outright quackery.

The Physician Examines the Bible. By C. Raimer Smith, M.D., D.N.B. 8°, cloth, 394 pp. New York: Philosophical Library, 1950.

Dr. Smith discusses medical allusions found in the Bible under a number of headings. They include medical subjects in the Old Testament, medical notes on the Apocrypha, alcoholic liquors, New Testament medical references, the scriptures in the atomic age and the temple of the body or the temple of health. The text concludes with medical concordances to the Apocrypha and the Old and the New Testament. There is a good index.

Serology with Lipid Antigen: With special reference to Kahn and universal reactions. By Reuben L. Kahn, M.S., D.Sc., associate professor, Department of Dermatology and Syphilology, University of Michigan Medical School, chief of Serology Laboratory and of Serologic Consultation Service, University Hospital, special consultant, United States Public Health Service, and consultant in serology, United States Naval Medical School. 8°, cloth, 327 pp., with 77 tables and 27 charts. Baltimore: Williams and Wilkins Company, 1950. $6.00.

This monograph discusses the serology of the lipid antigen in general and especially in syphilis. The text is divided into four parts. The first and fourth parts deal with the broad aspects of serology with lipid antigen, and particularly with the universal serologic reaction. The second and third parts discuss in detail the serology of syphilis with the Kahn procedures and the technic of the Kahn methods. There are author and subject indexes. The text is well printed on a light, soft, nonglare paper. The monograph should be in all collections on syphilis and serology.

Genetics and the Races of Man: An introduction to modern physical anthropology. By William C. Boyd, Ph.D., professor of immunochemistry, Boston University School of Medicine. 8°, cloth, 453 pp., with 52 illustrations and 63 tables. Boston: Little, Brown and Company, 1950. $6.00.

This new book on physical anthropology is well written and should be in all collections on genetics. The chapters on the blood groups, on the use of blood groups in human classification and on other human genes are of particular significance to medicine. The book is well published and should be in the reference collections of medical libraries.

Santa Claus, M. D. By W. W. Bauer, M.D. 8°, cloth, 266 pp. Indianapolis: Bobbs-Merrill Company, Incorporated, 1950. $2.75.

Dr. Bauer, director of health education of the American Medical Association, presents for the laity the twelve-point health program of the Association in terms understandable to any person. He disputes the claims of the advocates of compulsory health insurance that Americans are in bad health, and that they cannot afford medical care. In an appendix Dr. Bauer also reviews the accomplishments of the state medical societies in the interest of public health. There are also lists of pamphlets available for free distribution from the headquarters of the Council on Medical Service in Chicago. An index should have been provided for the book, but otherwise the publishing is good. The volume should be in all public and medical libraries.

Selected Studies on Arteriosclerosis. By Rudolf Altschul, M.U.Dr., professor of histology, University of Saskatchewan, Saskatoon, Canada. 8°, cloth, 181 pp., with 79 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $5.50.

In this monograph the author presents twelve studies on various aspects of human and experimental arteriosclerosis. There are chapters on the experimental ligature of arteries, systematic description of cholesterolosis in tissues and organs, and results from modified experimental approaches. A bibliography concludes the text, and there are indexes of authors and subjects. The plate work is excellent. The monograph should be in all collections on the subject.

Grundsätzliches zur Diabetestherapie. Diskussion zu einem Merkblatt von Professor Dr. F. Bertram, Hamburg. Herausgegeben vom Deutschen Insulin-Komitee. 8°, paper, 40 pp. Stuttgart: Georg Thieme, 1950. Kartoniert DM 1.–

This pamphlet provides the latest information on the treatment of diabetes, especially on the use of insulin. It is written by 10 German specialists and should be in all collections on diabetes.

Language for the Preschool Deaf Child. By Grace H. Lassman, teacher of the deaf. With forewords by Dr. S. R. Silverman and Mrs. Harriet Montague. 8°, cloth, 263 pp., with 27 plates. New York: Grune and Stratton, 1950. $5.50.

In this book the author describes her methods of teaching for the benefit of teachers and parents of deaf children. After an introduction on deafness in childhood as a problem and responsibility, the text is divided into three parts: fundamentals of training; activities for language development; and the nursery school for deaf children and parent education. A bibliography of 223 references is appended to the text. There

is a good index, and the publishing is excellent. The book should be in all collections on deafness.

Plasma Clot Suture of Peripheral Nerves and Nerve Roots — Rationale and Technique. By I. M. Tarlov, M.D., associate professor of neurosurgery, New York Medical College, New York City. 8°, cloth, 116 pp., with 46 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $5.50.

This monograph discusses the various aspects of this particular neurosurgical procedure. There is an extensive bibliography and a good index. The illustrations are excellent. The book should be in all collections on neurosurgery.

Reports on Biological Standards. VI. The Design of Toxicity Tests. By W. L. M. Perry. 8°, paper, 51 pp., with 16 tables. London: His Majesty's Stationery Office, 1950. (Medical Research Council Special Report Series No. 270.) 1 shilling, 6 pence.

In this small monograph the author discusses the value of quantal response and the graded response methods.

History of The Woman's Medical College, Philadelphia, Pennsylvania, 1850–1950. By Gulielma F. Alsop, M.D., Woman's Medical College of Pennsylvania. 8°, cloth, 256 pp., with six illustrations and frontispiece. Philadelphia: J. B. Lippincott Company, 1950. $4.00.

The college whose history is here given was the first medical college for women in the United States. The story is well told in a narrative style supplemented by pertinent quotations from former writings on medical education and on the school. There is an index, and the book is well published. It should be in all collections on American medical history.

Renal Function: Transactions of the First Conference, October 20-21, 1949, New York, New York. Edited by Stanley E. Bradley, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 172 pp., with 40 illustrations. New York: Josiah Macy, Jr., Foundation, 1950. $2.50.

Fourteen physicians and a number of invited guests participated in this new conference sponsored by the Josiah Macy, Jr., Foundation. The topics discussed were the morphologic aspects of renal tubular processes, biochemical aspects of renal tubular transport, the role of glutaminase in tubular processes, the tubular secretion of potassium and acid and water reabsorption by the renal tubules. This new series should be in all medical libraries.

Das Strichbild: zum Form- und Stoffproblem in der Psychologie der Handschrift. Dr. med. R. Pophal, professor of graphology, University of Hamburg. 8°, paper, 60 pp., with 19 tables. Stuttgart: Georg Thieme, 1950. Kartoniert DM 6.60. Distributed by Grune and Stratton, New York.

This small monograph deals with the psychologic study of handwriting.

Bronconeumopatías micóticas (sudotuberculosis) en los obreros de la industria textil; su importancia en medicina del trabajo. 12°, paper, 55 pp., with 4 illustrations. Buenos Aires: Lopez and Etchegoyen, S.R.L., 1950.

This small monograph on microbic bronchopneumonia and its occurrence in workers in the textile industry is well arranged and well written. The text proper is preceded by a short historical sketch.

Plasma Proteins. Edited by John B. Youmans, M.D., dean and professor of medicine, Vanderbilt University School of Medicine. 8°, cloth, 352 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1950. $6.50. (Symposia on Nutrition of the Robert Gould Research Foundation, Incorporated, Vol. II.)

This volume contains papers by 21 contributors to the symposium on nutritional subjects held in Chicago, September 23-24, 1949, under the auspices of the University of Illinois College of Medicine. There are 18 papers on the plasma proteins in various aspects. Bibliographies are appended to the various papers. There is not an index; otherwise, the book is well published, and it should be in all medical libraries and biochemical collections.

Bibliography of Electroencephalography, 1875–1948. Edited by Mary A. B. Brazier. 4°, cloth, 178 pp. Montreal: Thérien Frères Limitée, for the International Federation of Electroencephalography and Clinical Neurophysiology, 1950. $5.00.

The references in this important bibliography have been compiled in seventeen subject categories and arranged alphabetically in each division. There is an author index, but the bibliography will be difficult to use because of its arrangement. There should have been a chronologic list in addition to the subject lists. The title page indicates that the earliest reference is 1875, but there is no indication where it and other early references may be found in the bibliography. The book should be in all medical libraries and in all collections on neuropsychiatry.

Venereal-Disease Control in the USA: With special reference to penicillin in early, prenatal, and infantile syphilis. Report of the WHO Syphilis Study Commission. 8°, paper, 69 pp. Geneva: World Health Organization, 1950. $0.45. (World Health Organization, Technical Report Series No. 15.)

This report presents the findings of the special Syphilis Study Commission of the WHO, consisting of 7 members, on venereal-disease control in the United States with special reference to the use of penicillin in early, prenatal and infantile syphilis. It should be in all collections on the subject.

The Other Side of the Bottle. By Dwight Anderson, with Page Cooper. 8°, cloth, 258 pp. New York: A. A. Wyn, Incorporated, 1950. $3.00.

This story was written by an alcoholic addict who was cured eighteen years ago. He tells his own experience, and then deals with alcoholism in general, and with the various treatments that have been proposed down through the years. The book should be in all collections on alcoholism.

Problems of Infancy and Childhood: Transactions of the Third Conference, March 7-8, 1949, New York, New York. 8°, cloth, 156 pp. New York: Josiah Macy, Jr., Foundation, 1949. $1.25.

Three topics were discussed at this conference: anxieties of mothers as described to physicians; the psychologic situation of mother and child upon return from the hospital; and observations on the emotional reactions of children to tonsillectomy and adenoidectomy. Twenty-four persons took part in the conference.

Neurosis and Psychosis. By Beulah C. Bosselman, M.D., associate professor of psychiatry, University of Illinois College of Medicine. With a foreword by Francis J. Gerty, M.D., professor of psychiatry and head, Department of Psychiatry, University of Illinois College of Medicine. 8°, cloth, 172 pp. Springfield, Illinois: Charles C Thomas, 1950. $4.50.

The material in this book is based on a series of lectures given each year since 1940 to medical and postgraduate students at the University of Illinois College of Medicine. The author discusses first the general states, such as the various types of hysteria, and proceeds gradually to the more complicated processes of the organic psychoses. The final chapter is devoted to psychosomatic medicine. The book is well published and should be in all collections on psychiatry.

Urgent Diagnosis Without Laboratory Aid: A discussion of the external signs of conditions which threaten life. By Prof. Dr. Hanns L. Baur, a.o. professor of internal medicine, University of Munich. 8°, cloth, 89 pp. Springfield, Illinois: Charles C Thomas, 1950. $2.00.

This monograph discusses the clinical signs of various types of disease. The text is divided into seven sections dealing with nervous manifestations, including unconsciousness and psychoses, and convulsions; facies, position and attitude; abnormal odors, cutaneous manifestations; disorders of respiration; urinary symptoms; and gastrointestinal manifestations.

(*Notices on page xv*)